10593180

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/009595

International filing date: 21 March 2005 (21.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/554,571
Filing date: 19 March 2004 (19.03.2004)

Date of receipt at the International Bureau: 02 May 2005 (02.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
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APPLICATION NUMBER: *60/554,571*
FILING DATE: *March 19, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US05/09595*

Certified by

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Attorney's Docket No. 5062.00
Express Mail Label No. EV 329268595 US

PATENT

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Mail Stop Provisional Patent Application
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This is a request for filing a PROVISIONAL PATENT APPLICATION under 37 C.F.R. 1.53(c).

Docket No.	5062.00
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TITLE OF THE INVENTION

PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING NEURODEGENERATIVE DISORDERS

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ENCLOSED APPLICATION PARTS

Specification (Number of Pages: 80)
Claims (Number of Claims: 1)
Drawings (Number of Pages: 0)
Application Data Sheet under 37 CFR 1.76 (Number of Pages: 2)
Self-addressed Postcard Receipt

METHOD OF PAYMENT

The Commissioner is hereby authorized to charge filing fees and credit any overpayment to **Deposit Account No. 50-1627**

PROVISIONAL FILING FEE AMOUNT

Large Entity $160.00

Filing Fee Amount: $160

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PHARMACEUTICAL COMPOSITION AND METHOD FOR TREATING NEURODEGENERATIVE DISORDERS

TECHNICAL FIELD OF THE INVENTION

The invention provides a method for the therapeutic treatment of neurodegenerative disorders. The invention further provides a method for prophylaxis against neurodegenerative disorders. The invention further provides pharmaceutical composition for use in the methods of the invention. The invention has utility for treating and preventing neurodegenerative disorders such as Alzheimer's disease, dementia, and mild cognitive impairment.

BACKGROUND OF THE INVENTION

Dementia is a brain disorder that seriously affects a person's ability to carry out normal daily activities. Among older people, Alzheimer's disease (AD) is the most common form of dementia and involves parts of the brain that control thought, memory, and language. Despite intensive research throughout the world, the causes of AD are still unknown and there is no cure. AD most commonly begins after the age of 60, with the risk of acquiring the disease increasing with age. Younger people can also get AD, but it is much less common. It is estimated that 3 percent of men and women ages 65 to 74 have AD. Almost half of those ages 85 and older may have the disease. AD is not a normal part of aging. Alzheimer's disease is a complex disease that can be caused by genetic and environmental factors.

In 1906, Dr. Alois Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. In her brain tissue, he found abnormal clumps (now known as amyloid plaques) and tangled bundles of fibers (now known as neurofibrillary tangles) which, today, are considered the pathological hallmarks of AD. Other brain changes in people with AD have been discovered. For example, with AD, there is a loss of nerve cells in areas of the brain that are vital to memory and other

mental abilities. Scientists have found that there are lower levels of chemicals in the brain that carry complex messages back and forth between nerve cells. AD may disrupt normal thinking and memory by blocking these messages between nerve cells.

Plaques and tangles are found in the same brain regions that are affected by neuronal and synaptic loss. Neuronal and synaptic loss is universally recognized as the primary cause of decline in cognitive function in AD patients. The number of tangles is more highly correlated with cognitive decline than amyloid load in patients with AD (Albert *PNAS* 93:13547-13551 (1996)). The cellular, biochemical, and molecular events responsible for neuronal and synaptic loss in AD are not known. A number of studies have demonstrated that amyloid can be directly toxic to neurons resulting in behavioral impairment (*see, e.g.,* Iversen *et al. Biochem. J.* 311:1-16 (1995); Weiss *et al. J. Neurochem.* 62:372-375 (1994); Lorenzo *et al. Ann N Y Acad. Sci.* 777:89-95 (1996); and Storey *et al. Neuropathol. Appl. Neurobiol.* 2:81-97 (1999)). The toxicity of amyloid or tangles is potentially aggravated by activation of the complement cascade (Rogers *et al. PNAS* 21:10016-10020 (1992); Rozemuller *et al. Res. Immunol.* 6:646-9 (1992); Rogers *et al. Res Immunol.* 6:624-30 (1992); and Webster *et al. J. Neurochem.* 69(1):388-98 (1997)). This suggests involvement of an inflammatory process both in AD and the neuronal death seen in AD (*see, e.g.*, Fagarasan *et al. Brain Res.* 723(1-2):231-4. (1996); Kalaria *et al. Neurodegeneration.* 5(4):497-503 (1996); Kalaria *et al. Neurobiol Aging.* 17(5):687-93 (1996); and Farlow *Am J Health Syst Pharm.* 55 Suppl. 2:S5-10 (1998)).

Evidence that amyloid β protein (Aβ) deposition causes some forms of AD was provided by genetic and molecular studies of some familial forms of AD (FAD). (*See, e.g.*, li *Drugs Aging* 7(2):97-109 (1995); Hardy *PNAS* 94(6):2095-7 (1997); and Selkoe *J. Biol. Chem.* 271(31):18295-8 (1996)). The amyloid plaque buildup in AD patients suggests that abnormal processing of Aβ may be a cause of AD. Aβ is a peptide of 39 to 42 amino acids and is the core of senile plaques observed in all Alzheimer's disease cases. If abnormal processing is the primary cause of AD, then familial Alzheimer's disease (FAD) mutations that are linked (genetically) to FAD may induce changes that, in one way or another, foster Aβ deposition. Mutations in the FAD genes can result in

increased Aβ deposition. It is noted that the vast majority of Alzheimer's disease cases are not a result of mutations in FAD genes.

The first of the FAD genes codes for the Aβ precursor, amyloid precursor protein (APP) (Selkoe *J. Biol. Chem.* 271(31):18295-8 (1996)). Mutations in the APP gene are very rare, but all of them cause AD with 100% penetrance and result in elevated production of either total Aβ or $A\beta_{42}$, both in model transfected cells and transgenic animals. Two other FAD genes code for presenilin 1 and 2 (PS1, PS2) (Hardy *PNAS* 94(6):2095-7 (1997)). The presenilins contain 8 transmembrane domains and several lines of evidence suggest that they are involved in intracellular protein trafficking. Other studies suggest that the presenilins function as proteases. Mutations in the presenilin genes are more common than in the APP genes, and all of them also cause FAD with 100% penetrance. Similar to APP mutants, studies have demonstrated that PS1 and PS2 mutations shift APP metabolism, resulting in elevated $A\beta_{42}$ production (*in vitro* and *in vivo*).

Cyclooxygenases (COX) are major Alzheimer's disease drug targets due to the epidemiological association of NSAID use, whose primary target are cycloxygenases, with a reduced risk of developing Alzheimer's disease (*see, e.g.*, Hoozemans *et al. Curr. Drug Targets* 4(6):461-8 (2003) and Pasinetti *et al. J. Neurosci. Res.* 54(1):1-6 (1998)). The epidemiological studies have indicated that chronic NSAID use appears to reduce the risk of acquiring Alzheimer's disease and/or delay the onset of the disease. COX-2 selective inhibitors are attractive candidates for long-term drug use since they do not inhibit COX-1 and appear to be less toxic. In support of COX-2 being a target for treating AD, a recent study was published reporting that in mouse models of AD, COX-2 overexpression was related to the neuropathology of AD (Xiang *et al. Neurobiol. Aging* 23:327-34 (2002)). At the 8th international conference on Alzheimer's disease and related disorders, it was reported that rofecoxib, a COX-2 selective NSAID, at 25 mg daily, failed to show efficacy for treating AD. Naproxen, a nonselective COX inhibitor, in the same trial failed to show efficacy in Alzheimer's disease treatment (see Aisen *et al.* (*JAMA* 289:2819-26 (2003)). These authors concluded that the results with naproxen and rofecoxib do not support the use of NSAIDs for the treatment of AD. Lastly, rofecoxib failed, in a large prevention clinical trial, to prevent the development of

Alzheimer's disease in patients having mild cognitive impairment. In fact, the results of this trial showed that 6.4% of patients taking rofecoxib developed AD as compared to 4.5% for those taking placebo (*see e.g.*, Visser *et al.*, abstract from Annual meeting of the American College of Neuropsychopharmacology San Juan, Puerto Rico, 2003; and Landers, *Wall Street Journal* 10 Dec. 2003.) Thus, clinical trials have indicated that NSAIDs, as a general class of drugs, are not likely to be useful for treating and/or preventing Alzheimer's disease.

Aβ formation is another target for affecting Alzheimer's disease progression since Aβ amyloid plaques are a central pathological hallmark of the disease. Recently, it was suggested that certain NSAIDs are capable of lowering the level of Aβ_{42}. United States Patent Application 2002/0128319 to Koo *et al.* discloses the use of an Aβ_{42} lowering amount of NSAID for treating Alzheimer's disease. The hope is that by lowering the level of Aβ_{42}, the formation of the amyloid plaques central to the disease would be retarded. Interestingly, several studies have pointed to a link between amyloid plaque formation and COX-2 overexpression (*see, e.g.*, Xiang *et al. Gene Expr.* 10(5-6):271-8 (2002)).

A recent clinical trial using a therapy designed to eliminate Aβ plaques from disease patients failed despite strong evidence of efficacy in animal models (Pieffer *et al. Science* 298:1379 (2002)). The Aβ-lowering therapy that worked in animal models caused serious problems in humans. In view of the clinical studies, Atwood *et al.* (*Science* 299:1014 (2003)) noted that "Mounting evidence indicates that this deposition of amyloid-β may be a neuroprotective response to injury" and "These results demonstrate yet again the futility of removing a protein, amyloid-β, which has ubiquitous tissue expression, without first understanding its function(s)." Additionally, secretase inhibitors, which were designed to alter processing of APP, have turned out to be toxic compounds not likely to be suitable for chronic human use. Thus, it is not clear if reducing Aβ or Aβ_{42} is a realistic treatment/prevention option. Indeed, as noted recently, mutations in PS-1 associated with AD may cause the disease not through altering Aβ processing but rather by affecting calcium homeostasis (Mattson *Nature* 442:385-386 (2003)).

Several epidemiological studies have reported an association between long-term use of NSAIDs, such as ibuprofen and aspirin, with reduced risk for certain malignancies and neurodegenerative processes characterized by dementia of the Alzheimer's type. A variety of explanations have been given for the reduced cancer and Alzheimer's disease (AD) risk associated with long-term NSAID use. The primary action of NSAIDs appears to be inhibition of cyclooxygenase (COX) activity. Thus, a leading hypothesis is that NSAIDs reduce risk for certain cancers and Alzheimer's disease by affecting the COX enzymes. Other explanations include mediation of apoptosis, modulation of growth factors, and modulation of the nuclear factor kappa B pathway (NF-κB).

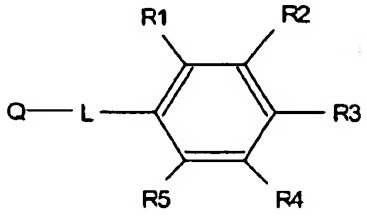
United States Patent No. 5,192,753 to McGeer *et al.* discloses the use of NSAIDs to treat Alzheimer's disease through the inhibition of cyclooxygenase and therefore inhibition of prostaglandin synthesis. United States Patent Nos. 5,643,960 and 6,025,395 both to Brietner *et al.* disclose the use of COX inhibiting NSAIDs to delay the onset of Alzheimer's disease. Despite the incredible wealth of information regarding NSAID use and its link to a reduced risk of developing Alzheimer's disease, there is no Food and Drug Administration (FDA) approved NSAID indication for Alzheimer's disease or any other equivalent national approval agency. Furthermore, several promising NSAIDs have failed in clinical trial designed to test their efficacy in treating AD.

In the United States alone, four million adults suffer from Alzheimer's disease (AD). Not only is Alzheimer's disease significantly impacting the lives of countless families today, it is threatening to become even more of a problem as the baby boom generation matures. The economic burden of AD is estimated to cost over $100 billion a year and the average lifetime cost per patient is estimated to be $174,000. Unfortunately, there is no cure available for AD. Of the five drugs currently being used in the US for the treatment of AD, four of them - tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®), are inhibitors of acetylcholine esterase. Another drug, memantine, was recently approved for treating moderate-to-severe AD. More recently it was reported that memantine showed efficacy in treating mild-to-moderate AD. Memantine is a NMDA receptor antagonist.

The drugs currently used for treating AD, including memantine and the acetylcholine esterase inhibitors, are marginally efficacious and have undesirable side-effects. Thus, there is a large unmet need for better and safer drugs.

SUMMARY OF THE INVENTION

In general, the invention relates to the use of compounds of Formula I-IV, for the treatment and prophylaxis of neurodegenerative disorders. In a first aspect, the invention provides compounds of Formula I-IV, pharmaceutically acceptable salts thereof, and pharmaceutical compositions having such compounds:

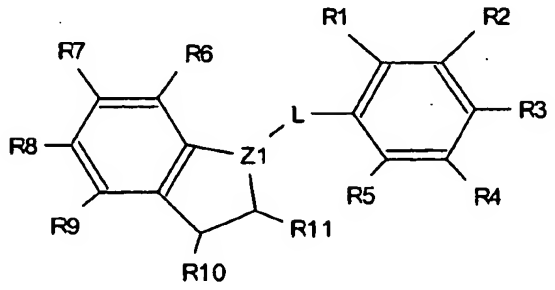


FORMULA I

wherein R1-R5, independent of one another, are selected from the group consisting of hydro, hydroxyl, halo, alkyl, alkoxy, haloalkyl, -CN, $-NH_2$, $-NO_2$, $-C(=O)OH$, $-CH(CH_3)C(=O)OH$, $-CH(CH_2CH_3)C(=O)OH$, $-C(CH_3)(CH_2CH_3)C(=O)OH$, $-CH=C(CH_3)C(=O)OH$, $-C(CH_2CH_3)_2C(=O)OH$ $-CH_2OH$, $-C(=O)H$, $-CH(OH)OCH_3$, $-CH(CH_3)$tetrazole, $-CH_2C(=O)OH$, $-C(CH_3)_2C(=O)OH$, and $-NHC(=O)CH_3$;

L is a linker which can be a direct bond between Q and the ring system, or is selected from $-(CH_2)_n-$, –NH-, -O-, -S-, $-NH-CH(CH_3)-$, $-NH-CH(CH_3)-CH_2-$, $-NH-CH(CH_3)-CH_2-CH_2-$,$-NH-CH_2-CH(CH_3)-$, and $-NH-CH_2-CH_2-CH(CH_3)-$, $-(CH_2)_nC(=O)(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, where each n is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, and 8;

Q is selected from the group consisting of optionally substituted aryl, optionally substituted heterocycle, optionally substituted heteroaryl, and optionally substituted cycloalkyl;



FORMULA II

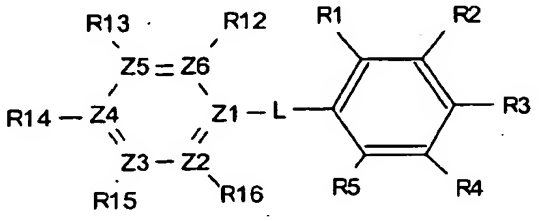
wherein R1-R5 are as defined above;

R6-R11, independent of one another, are selected from the group consisting of hydro, hydroxyl, halo, alkyl, alkoxy, -CN, $-NH_2$, $-NO_2$, haloalkyl, -C(=O)OH, $-CH(CH_3)C(=O)OH$, $-CH(CH_2CH_3)C(=O)OH$, $-CH_2OH$, -C(=O)H, $-CH(OH)OCH_3$, $-CH(CH_3)$tetrazole, $-CH_2C(=O)OH$, $-C(CH_3)_2C(=O)OH$, and $-NC(=O)CH_3$;

Z1 is -CH- or –N-, provided that Z1 is not –N- when L is –O-, -S-, or –NH-;

L is as defined above;

and there is a single or double bond between the carbons attached to R10 and R11;



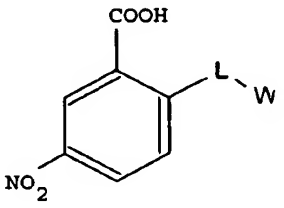
FORMULA III

wherein R1-R5 are as defined above;

R12-R16, independent of one another, are selected from the group consisting of hydro, hydroxyl, halo, alkyl, alkoxy, -NH_2, -NO_2, haloalkyl, -C(=O)OH, -$CH(CH_3)$C(=O)OH, -$CH(CH_2CH_3)$C(=O)OH, -CH_2OH, -C(=O)H, -$CH(OH)OCH_3$, -$CH(CH_3)$tetrazole, -CH_2C(=O)OH, -$C(CH_3)_2$C(=O)OH, -NC(=O)CH_3;

Z1-Z6, independent of one another, are selected from –C- or –N-, provided that Z1 is not –N- when L is –O-, -S-, or –NH-; and

L is as defined above;



Formula IV

wherein L is selected from the group consisting of a bond,–CH_2-, –NH-, -O-, S, –NH-CH_2-, –NH-CH_2-CH_2-, –NH-CH_2-CH_2-CH_2-, –NH-$CH(CH_3)$-, –NH-$CH(CH_3)$-CH_2-, –NH-$CH(CH_3)$-CH_2-CH_2-, –NH-CH_2-$CH(CH_3)$-, –NH-CH_2-CH_2-$CH(CH_3)$-, -$(CH_2)_n$C(=O)$(CH_2)_n$-, -$(CH_2)_n$NH$(CH_2)_n$-, -$(CH_2)_n$O$(CH_2)_n$-, and -$(CH_2)_n$S$(CH_2)_n$-, where each n is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, and 8; W is selected from the group consisting of hydro, optionally substituted cycloalkyl, optionally substituted heterocycle, optionally substituted heteroaryl, and optionally substituted indane.

In a second aspect, the invention provides a method of treating a neurodegenerative disorder, by identifying a patient in need of such treatment, and administering to the patient a therapeutically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Administration of a compound of Formula I-IV for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, can provide an improvement or lessening in decline of cognitive function as characterized by cognition tests, biochemical disease marker progression, and/or plaque pathology. Cognition tests are those which are capable of measuring cognitive decline in a patient or group of patients. Examples of such cognition tests include the ADAS-cog (Alzheimer's Disease Assessment Scale, cognitive

subscale) NPI (Neuropsychiatric Inventory), ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living), CIBIC-plus (Clinician Interview Based Impression of Change), and CDR sum of boxes (Clinical Dementia Rating). It is preferred that the lessening in decline in cognitive function is at least 25 % as compared to individuals treated with placebo, more preferably at least 40 %, and even more desirably at least 60 %. For example, an individual treated with placebo having probable mild-to-moderate Alzheimer's disease is expected to score approximately 5.5 points worse on the ADAS-cog test after a specified period of time of treatment (*e.g.*, 1 year) whereas an individual treated with the composition of this aspect of the invention for the same period of time will score approximately 2.2 points worse on the ADAS-cog scale with a 60% decrease in decline or 3.3 points worse with a 40% decrease in decline in cognitive function when treated with the composition for the same specified period of time. Desirably, the oral dose is provided in capsule or tablet form. The pharmaceutical composition for use in the invention is formulated with one or more pharmaceutically acceptable excipients, salts, or carriers. The pharmaceutical composition for use in the invention is delivered orally, preferably in a tablet or capsule dosage form.

In a third aspect, the invention provides a method for prophylaxis against a neurodegenerative disorder, by identifying a patient in need of or desiring such treatment, and administering to the patient a prophylactically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Administration of a compound of Formula I-IV for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, can delay the onset of the neurodegenerative disorder or slow the rate of onset of symptoms of the disorder. Patients having a predisposition to a neurodegenerative disorder or suspected of needing prophylaxis can be identified by any method known to the skilled artisan for diagnosis such neurodegenerative disorders.

In a fourth aspect, the invention provides a method of treating a disease characterized by abnormal amyloid precursor protein processing by (1) identifying a patient in need of such treatment, and (2) administering to the patient a therapeutically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Oral administration of the pharmaceutical composition for use in the method of this aspect the invention for at least 4 weeks, preferably at least 4 months, and

more desirably at least 8 months, provides an improvement or lessening in decline of cognitive function as characterized by cognition tests, biochemical disease marker progression, and/or plaque pathology. Examples of biochemical disease markers include, for example, amyloid beta peptide ($A\beta$), $A\beta_{42}$, and tau. It is preferred that the lessening in decline in biochemical disease marker progression is at least 10 % as compared to individuals treated with placebo, more preferably at least 20 %, and more desirably at least 40 %. It is preferred that the lessening in decline in cognitive function is at least 25 % as compared to individuals treated with placebo, more preferably at least 40 %, and even more desirably at least 60 %. Desirably, the composition is provided as an oral dose, preferably in capsule or tablet form.

In a fifth aspect, the invention provides a method of prophylaxis or delaying the onset of a disease (or one or more symptoms thereof) characterized by abnormal amyloid precursor protein processing, by identifying a patient in need of such treatment and administering to the patient a prophylactically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Oral administration of the pharmaceutical composition for use in the method of this aspect the invention for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, prevents or delays the onset of the disease (or symptoms thereof) characterized by abnormal amyloid precursor protein processing.

In a sixth aspect, the invention provides a method of treating Alzheimer's disease comprising administering to a patient in need of such treatment, a pharmaceutical composition having one or more compounds of Formula I-IV. Oral administration of the pharmaceutical composition for use in the method of this aspect of the invention for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, provides an improvement or lessening in decline of cognitive function as characterized by cognition tests, biochemical disease marker progression, and/or plaque pathology. Desirably, the oral dose is provided in capsule or tablet form. According to this aspect of the invention, a patient in need of treatment is administered an Alzheimer's disease treating effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV and one or more pharmaceutically acceptable salts, excipients and carriers. The method of this aspect of the invention involves identifying

an individual likely to have mild-to-moderate Alzheimer's disease. An individual having probable mild-to-moderate Alzheimer's disease can be diagnosed by any method available to the ordinary artisan skilled in such diagnoses. For example, diagnosis can be according to DSM IV (TR) and/or meets NINCDS-ADRDA criteria for probable AD. According to this aspect of the invention, individuals with probable mild-to-moderate AD take an oral dose of a pharmaceutical composition for a specified period of time. Individuals undergoing such treatment are likely to see an improvement or lessening in decline of cognitive function, an improvement or lessening in decline in biochemical disease marker progression, and/or an improvement or lessening decline in plaque pathology. A lessening in decline in cognitive function can be assessed using a test of cognitive function like the ADAS-cog. For example, an individual treated with placebo having probable mild-to-moderate Alzheimer's disease is expected to score approximately 5.5 points worse on the ADAS-cog test after a specified period of time of treatment (*e.g.*, 1 year) whereas an individual treated with the composition of this aspect of the invention for the same period of time will score approximately 2.2 points worse on the ADAS-cog scale with a 60% decrease in decline or 3.3 points worse with a 40% decrease in decline in cognitive function when treated with the composition for the same specified period of time. In a related aspect, the method involves identifying a patient having moderate-to-severe AD and administering to the patient an Alzheimer's disease treating effective amount of a compound of Formula I-IV.

In a seventh aspect, the invention provides a method of preventing the onset of Alzheimer's disease comprising administering to a patient in need of or desiring such treatment, a pharmaceutical composition having one or more compounds of Formula I-IV. Oral administration of the pharmaceutical composition for use in the method of this aspect of the invention for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, delays the onset of decline of cognitive function, biochemical disease marker progression, and/or plaque pathology. According to this embodiment, an individual desiring or needing preventative treatment against the onset of AD is administered a pharmaceutical composition having one or more compounds of Formula I-IV. Desirably, the oral dose is provided in capsule or tablet form. The preventive treatment is preferably maintained as long as the individual continues to desire or need

the treatment. Individuals needing or desiring preventative treatment against AD can be those having risk factors for developing AD. For example, risk factors for developing AD can be genetic factors or environmental factors. In one embodiment, the risk factor is age. Genetic risk factors can be assessed in a variety of ways, such as ascertaining the family medical history of the individual, or performing a genetic test to identify genes that confer a predisposition for developing AD. Additionally, risk factors can be assessed by monitoring genetic and biochemical markers.

The foregoing and other advantages and features of the invention, and the manner in which the same are accomplished, will become more readily apparent upon consideration of the following detailed description of the invention taken in conjunction with the accompanying examples, which illustrate preferred and exemplary embodiments.

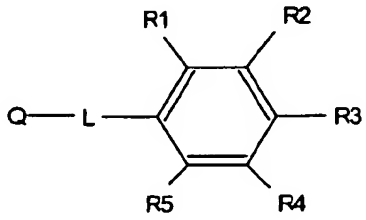
BRIEF DESCRIPTION OF THE DRAWINGS

N/A

DETAILED DESCRIPTION OF THE INVENTION

In general, the invention relates to the use of pharmaceutical compositions having one or more compounds of Formula I-IV as the active ingredient, for treating neurodegenerative disorders. When the pharmaceutical composition is administered, according to the treatment regimens of the invention, to an individual desiring or needing such treatment, it provides an improvement or lessening in decline of cognitive function, biochemical disease marker progression, and/or plaque pathology associated with neurodegenerative disorders such as AD. The composition of the invention is formulated with one or more pharmaceutically acceptable excipients, salts, or carriers. The pharmaceutical composition of the invention is delivered orally, preferably in a tablet or capsule dosage form. The pharmaceutical compositions can be used in methods for treating, preventing, and prophylaxis against neurodegenerative disorders such as Alzheimer's disease, and disease characterized by abnormal amyloid precursor protein processing.

The invention therefore provides compounds of Formula I-IV and pharmaceutical composition having such compounds, for the treatment and prophylaxis of neurodegenerative disorders:



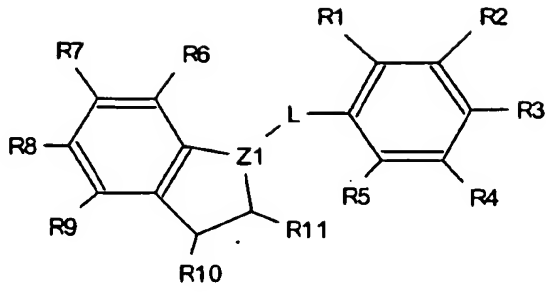
FORMULA I

wherein R1-R5, independent of one another, are selected from the group consisting of hydro, hydroxyl, halo, alkyl, alkoxy, haloalkyl, -CN, $-NH_2$, $-NO_2$, -C(=O)OH, $-CH(CH_3)C(=O)OH$, $-CH(CH_2CH_3)C(=O)OH$, $-C(CH_3)(CH_2CH_3)C(=O)OH$, $-CH=C(CH_3)C(=O)OH$, $-C(CH_2CH_3)_2C(=O)OH$ $-CH_2OH$, -C(=O)H, $-CH(OH)OCH_3$, $-CH(CH_3)$tetrazole, $-CH_2C(=O)OH$, $-C(CH_3)_2C(=O)OH$, and $-NHC(=O)CH_3$;

L is a linker which can be a direct bond between Q and the ring system, or is selected from the group consisting of $-(CH_2)_n-$, –NH-, -O-, -S-, –NH-$CH(CH_3)$-, –NH-$CH(CH_3)-CH_2$-, –NH-$CH(CH_3)-CH_2-CH_2$-, –NH-$CH_2-CH(CH_3)$-, –NH-$CH_2-CH_2-CH(CH_3)$-, $-(CH_2)_nC(=O)(CH_2)_n-$, $-(CH_2)_nNH(CH_2)_n-$, $-(CH_2)_nO(CH_2)_n-$, and $-(CH_2)_nS(CH_2)_n-$, where each n is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, and 8;

Q is selected from the group consisting of optionally substituted aryl, optionally substituted heterocycle, optionally substituted heteroaryl, and optionally substituted cycloalkyl; with the provisio that the compound is not flurbiprofen, R-flurbiprofen, S-flurbiprofen, or indomethacin.

A preferred subset of compounds of Formula I include those as in Formula II:



FORMULA II

wherein R1-R5 are as defined above;

R6-R11, independent of one another, are selected from the group consisting of hydro, hydroxyl, halo, alkyl, alkoxy, -CN, $-NH_2$, $-NO_2$, haloalkyl, -C(=O)OH, $-CH(CH_3)C(=O)OH$, $-CH(CH_2CH_3)C(=O)OH$, $-CH_2OH$, -C(=O)H, $-CH(OH)OCH_3$, $-CH(CH_3)$tetrazole, $-CH_2C(=O)OH$, $-C(CH_3)_2C(=O)OH$, and $-NC(=O)CH_3$;

Z1 is –CH- or –N-, provided that Z1 is not N when L is –O-, -S-, or –NH-;

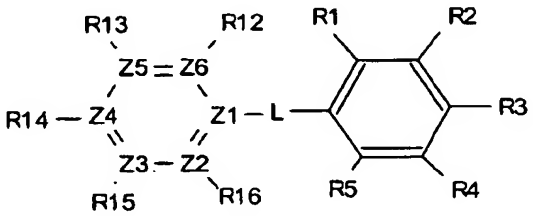
L is as defined above;

and there is a single or double bond between the carbons attached to R10 and R11 with the provisio that the compound is not indomethacin.

A preferred subset of compounds of Formula II include those where L is selected from the group consisting of $-CH_2-$ and –C(=O)-; Z1 is nitrogen; R1 is hydro; R2 is selected from the group consisting of hydro, lower alkoxy, and halo (if halo then preferably chloro); R3 is selected from the group consisting of hydro, lower alkoxy, halo, haloalkyl, $-CHF_2$, $-O-CF_3$, $-S-CF_3$, and $-CF_3$; R4 is selected from the group consisting of hydro, lower alkoxy, and halo (if halo then preferably chloro); R5 is hydro; R6 is hydro; R7 is hydro; R8 is selected from hydro and $-C(CH_3)_3$; R10 is $-CH_2C(=O)OH$; R11 is $-CH_3$; with the provision that the compound is not indomethacin. Additionally, R2 and R3, or R3 and R4 can be taken together to form a 5 or 6 membered heterocyclic ring (preferably $-O-CH_2-O-$ or $-O-CF_2-O-$). In a preferred subset of this subset, when R3 is not hydro, then R2 and R4 are halogen (preferably chloro). In another preferred subset of this subset, when R2 and R4 are both hydro, then R3 is selected from the group consisting of $-O-CF_3$, $-S-CF_3$, and $-CF_3$.

Another preferred subset of compounds of Formula II include those where L is selected from the group consisting of -CH_2- and –C(=O)-; Z1 is nitrogen; R1 is hydro; R2 is selected from the group consisting of hydro and halo (if halo then preferably chloro); R3 is selected from the group consisting of hydro; -O-CF_3, -S-CF_3, and -CF_3; R4 is selected from the group consisting of hydro and halo (if halo then preferably chloro); R5 is hydro; R6 is hydro; R7 is hydro; R8 is selected from hydro and –$C(CH_3)_3$; R10 is selected from the group consisting of -$CH_2C(=O)OCH_2C(=O)OH$ and -$CH_2C(=O)OH$; R11 is -CH_3; with the provision that the compound is not indomethacin. Preferably, when R3 is not hydro then R2 and R4 are halogen (preferably chloro). Preferably, when R2 and R4 are both hydro then R3 is selected from the group consisting of -O-CF_3, -S-CF_3, and -CF_3.

A preferred subset of compounds of Formula I include those of Formula III:



FORMULA III

wherein R1-R5 are as defined above;

R12-R16, independent of one another, are selected from the group consisting of hydro, hydroxyl, halo, alkyl, alkoxy, -NH_2, -NO_2, haloalkyl, -C(=O)OH, -$CH(CH_3)C(=O)OH$, -$CH(CH_2CH_3)C(=O)OH$, -CH_2OH, -C(=O)H, -$CH(OH)OCH_3$, -$CH(CH_3)$tetrazole, -$CH_2C(=O)OH$, -$C(CH_3)_2C(=O)OH$, and -$NC(=O)CH_3$;

Z1-Z6, independent of one another, are selected from C or N, provided that Z1 is not N when L is –O-, -S-, or –N-; and

L is as defined above.

A preferred subset of compounds of Formula III for use in the invention include those where L represents a bond; Z1-Z6 are each C; R1 is hydro; R2 is selected from the group consisting of hydro, -C(=O)OH, -$CH(CH_3)C(=O)OH$; R3 is selected from the

group consisting of hydro, -$CH_2C(=O)OH$, -$CH(CH_3)C(=O)OH$, -$C(CH_3)_2C(=O)OH$, -$C(CH_3)(CH_2CH_3)C(=O)OH$, -$CH(CH_2CH_3)C(=O)OH$, -$CH=C(CH_3)C(=O)OH$, and -$C(CH_2CH_3)_2C(=O)OH$; R4 is selected from the group consisting of hydro, -$CH_2C(=O)OH$, -$CH(CH_3)C(=O)OH$, -$C(CH_3)_2C(=O)OH$, and -$C(CH_2CH_3)_2C(=O)OH$; R5 is selected from the group consisting of hydro or halo (if halo then preferably fluoro); R12 and R16 are each independently selected from the group consisting of halo and hydro; R13 and R15 are each independently selected from hydro and halo (if halo then preferably chloro); R14 is selected from the group consisting of hydro, halo, methoxy, and lower alkoxy; with the provision that the compound is not flurbiprofen, R-flurbiprofen, or S-flurbiprofen.

Another preferred subset of compounds of Formula III for use in the invention include those where L represents a bond; Z1-Z6 are each a carbon; R5 is selected from the group consisting of hydro or halo (if halo then preferably fluoro); R1 and R2 are each hydro; R3 is selected from the group consisting of hydro, -$C(CH_3)_2C(=O)OH$, and -$C(CH_2CH_3)_2C(=O)OH$; R4 is selected from the group consisting of hydro, -$CH_2C(=O)OH$, -$CH(CH_3)C(=O)OH$, -$C(CH_3)_2C(=O)OH$, and -$C(CH_2CH_3)_2C(=O)OH$; R12 and R16 are each hydro; R13 and R15 are selected from hydro and halo (if halo then preferably chloro); R14 is selected from the group consisting of hydro, methoxy, and lower alkoxy.

In another preferred subset of compounds of Formula III, L is selected from the group consisting of -O- and –NH-; R1 is selected from the group consisting of hydro, -$CH_2C(=O)OH$, -$CH(CH_3)C(=O)OH$, -$C(CH_3)_2C(=O)OH$, -$C(CH_2CH_3)_2C(=O)OH$, and -$C(=O)OH$; R2 is selected from the group consisting of hydro, -$CH_2C(=O)OH$, -$CH(CH_3)C(=O)OH$, -$C(CH_3)_2C(=O)OH$, -$C(CH_2CH_3)_2C(=O)OH$, and -$C(=O)OH$; R3 is hydro; R4 is hydro; R5 is hydro; R12 is selected from hydro or halo (if halo then preferably chloro); R13 is selected from hydro, halo (if halo then preferably chloro), -CF_3, and –CH_3; R14 is hydro; R15 is hydro or halo (if halo then preferably chloro); and R16 is hydro or halo (if halo then preferably chloro).

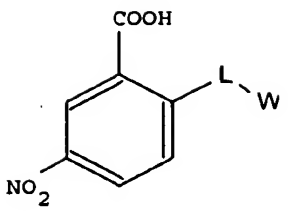
In yet another preferred subset of compounds of Formula III for use in the invention, L is –NH-CH_2-; R1 is hydro; R2 is selected from halo, -CH_3, and -CF_3; R3 is hydro or halo (if halo then preferably chloro); R4 is selected from halo, -CH_3, and -CF_3;

R5 is hydro; R12 is -C(=O)OH; R13 is hydro, R14 is $-NO_2$; R15 is hydro; and R16 is hydro.

In still another preferred subset of compounds of Formula III for use in the invention, L is selected from $-NH-CH_2-$, $-NH-CH_2-CH_2-$, $-NH-CH_2-CH_2-CH_2-$, $-NH-CH(CH_3)-$, $-NH-CH(CH_3)-CH_2-$, $-NH-CH(CH_3)-CH_2-CH_2-$,$-NH-CH_2-CH(CH_3)-$, and $-NH-CH_2-CH_2-CH(CH_3)-$; R1 is selected from the group consisting of hydro and halo (if halo then preferably chloro); R2 is selected from the group consisting of hydro, halo, haloalkyl (preferably trifluoromethyl), alkoxy (preferably methoxy), alkyl (preferably methyl); R3 is selected from the group consisting of hydro, halo, and phenyl; R4 is selected from the group consisting of hydro, halo, haloalkyl (preferably trifluoromethyl), alkoxy (preferably methoxy), alkyl (preferably methyl); R5 is selected from the group consisting of hydro and halo (if halo then preferably chloro); R12 is -C(=O)OH; R13 is hydro; R14 is $-NO_2$; R15 is hydro; and R16 is hydro. Additionally, in this subset of compounds any two of R1-R5 can be taken together to form an optionally substituted aryl or heteroaryl ring.

Another preferred subset of compounds of Formula III for use in the invention include those where L is a bond, each of R1-R5 is independently selected from the group consisting of hydro or $-CH_2-C(=O)OH$; each of Z1-Z6 is independently selected from the group consisting of C or N; R12 is selected from the group consisting of lower alkoxy, methoxy, ethoxy, halo, fluoro, and chloro; R13 is selected from the group consisting of lower alkoxy, methoxy, ethoxy, halo, fluoro, and chloro; R14 is selected from the group consisting of lower alkoxy, methoxy, ethoxy, halo, fluoro, and chloro; R15 is selected from the group consisting of lower alkoxy, methoxy, ethoxy, halo, fluoro, and chloro; R16 is selected from the group consisting of lower alkoxy, methoxy, ethoxy, halo, fluoro, and chloro.

Another set of compounds useful in the methods of the invention include those of Formula IV:



Formula IV

wherein L is selected from the group consisting of a bond,–CH_2-, –NH-, -O-, –NH-CH_2-, –NH-CH_2-CH_2-, –NH-CH_2-CH_2-CH_2-, –NH-$CH(CH_3)$-, –NH-$CH(CH_3)$-CH_2-, –NH-$CH(CH_3)$-CH_2-CH_2-, –NH-CH_2-$CH(CH_3)$-, –NH-CH_2-CH_2-$CH(CH_3)$-, -$(CH_2)_nC(=O)(CH_2)_n$-, -$(CH_2)_nNH(CH_2)_n$-, -$(CH_2)_nO(CH_2)_n$-, and -$(CH_2)_nS(CH_2)_n$-, where each n is independently selected from 0, 1, 2, 3, 4, 5, 6, 7, and 8; W is selected from the group consisting of hydro, optionally substituted cycloalkyl, optionally substituted hetereocycle, and optionally substituted indane.

Some of the compounds of Formula I-IV, for use in the invention may exist as single stereoisomers (*i.e.*, essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the compounds that are optically active are used in optically pure form. Furthermore, some of the compound for use in the invention can exist as cis and trans geometric isomers all such isomers and mixtures thereof are intended to be within the scope of the present invention.

Additionally, the formulas are intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I-IV include compounds of the indicated structure in both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

In addition to compounds of Formula I-IV, the invention includes pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds.

Prodrugs and active metabolites of compound may be identified using routine techniques known in the art. See, e.g., Bertolini, G *et al., J. Med. Chem.*, 40, 2011-2016

(1997); Shan, D. *et al., J. Pharm. Sci.*, 86 (7), 756-767; Bagshawe K., *Drug Dev. Res.*, 34, 220-230 (1995); Bodor N;, *Advance in Drug Res.*, 13, 224-331 (1984); Bundgaard, H., Design of Prodrugs (Elsevier Press 1985); and Larsen, I. K., Design and Application of Prodrugs, Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

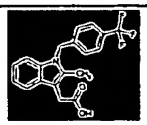
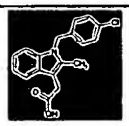
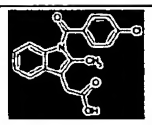
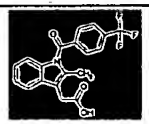
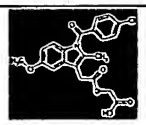
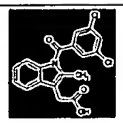
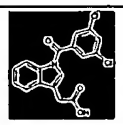
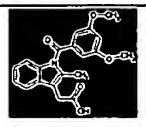
Methods of Prevention and Treatment

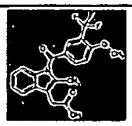
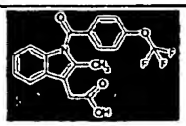
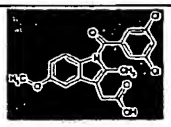
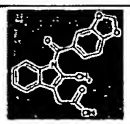
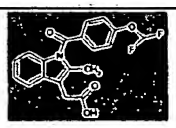
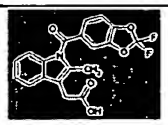
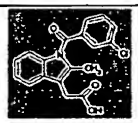
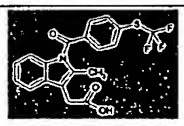
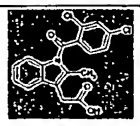
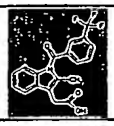
The invention provides methods for treating and/or preventing neurodegenerative disorders like AD and MCI, and lowering $A\beta_{42}$ in an individual in need of such treatment. It is believed that by lowering the amounts of $A\beta_{42}$ in an individual by administering an $A\beta_{42}$ lowering effective amount of a composition described herein, that Alzheimer's disease and mild cognitive impairment can be treated or prevented. Generally, the invention relates to the idea that compounds of Formula I-IV can be used to lower $A\beta_{42}$ levels. Thus, diseases characterized by increased levels of $A\beta_{42}$, can be treated or prevented with the methods of the invention which are designed to lower $A\beta_{42}$, prevent an increase in $A\beta_{42}$, and/or reduce the rate of increase of $A\beta_{42}$.

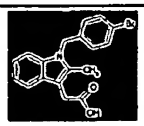
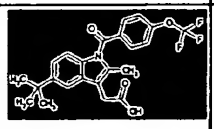
The invention is based on the fact that the inventors have discovered that compounds of Formula I-IV lower $A\beta_{42}$ levels in *in vitro* APP processing assays. Futhermore, compounds of Formula I-IV, in general, have negligible levels of COX inhibition and therefore are thought to essentially be devoid of the deleterious side-effects associated with COX inhibition. Thus, a preferred embodiment of the invention is the use of a pharmaceutical composition having one or more compounds of Formula I-IV, where the compound lowers $A\beta_{42}$ levels and does not substantial inhibit the cyclooxygenases. Preferred compounds of Formula I-IV for use in the invention are those that have little or negligible COX1 and/or COX2 inhibition at 1 μM, more preferred are those that little or negligible COX1 and/or COX2 inhibition at 10 μM, and more preferred are those that little or negligible COX1 and/or COX2 inhibition at 100 μM compound. COX1 and COX2 inhibition can be determined with a COX inhibitor screening kit from *e.g.*, Cayman Chemical, Ann Arbor, MI (Cat. # 560131). Using the Cayman chemical kit compounds 6, 10, 21, 38, 53, 60, and 68 were found to not significantly inhibit COX1 or COX2 at 100 μM. Particularly preferred compounds of

Formula I-IV for use in the methods and embodiments of the invention include those in Tables 1-5 below.

Table 1
$A\beta_{42}$ Lowering Compounds*

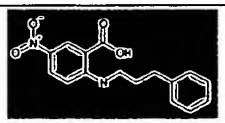
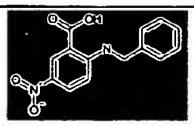
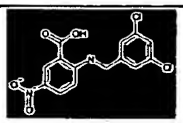
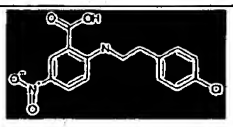
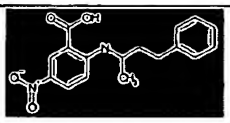
CMPD #	STRUCTURE	1H NMR, δ	MS DATA	NAME
1		δ 7-7.5 (8H,ArH), 5.3(2H,CH2), 2.3(3H,CH3), 3.7(2H,CH2)	neg.mode 346 (M-1), Pos.mode 348(M+1)	1-(4-trifluoromethylbenzyl)-2-methylindole-3-acetic acid
2		δ 6.8-7.5 (8H,ArH), 5.26(2H,CH2), 3.7(2H,CH2), 2.3(3H,CH3)	neg. mode 312 (M-1), pos.mode 314(M+1)	1-(4-chlorobenzyl)-2-methylindole-3-acetic acid
3		δ 7.6– 6.9 (8H,ArH), 3.7(2H,CH2),2.39(3H,CH3)	neg.mode 325.99(M-1)	1-(4-chlorobenzoyl)-2-methylindole-3-acetic acid
4		δ6.9-7.8 (8H,ArH), 3.7(2H,CH2), 2.3(3H,CH3)	neg.mode 360(M-1)	1-(4-trifluoromethylbenzoyl)-2-methylindole-3-acetic acid
5		Commercially available		
6		δ 6.9-7.6 (7H-ArH), 3.7(2H,CH2), 2.4(3H,CH3)	neg.mode 364(M-1)	1-(3,5-dichlorobenzoyl)-2-methylindole-3-acetic acid
7		δ 8.3 (1H), 7.5-7.2(7H,ArH), 3.7(2H,CH2)	neg.mode 347(M-1)	1-(3,5-dichlorobenzoyl)-3-indoleacetic acid
8		δ 7.2-6.8 (7H,ArH), 3.8 (6H,2CH3), 3.7(2H,CH2), 2.4 (3H,CH3)	neg.mode 352(M-1)	1-(3,5-dimethoxybenzoyl)-2-methylindole-3-acetic acid

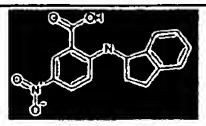
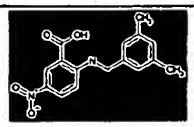
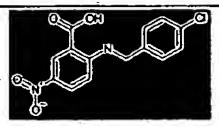
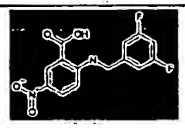
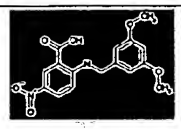
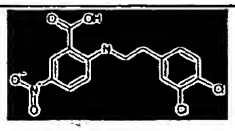
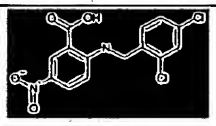
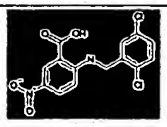
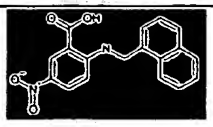
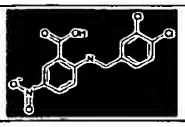
CMPD #	STRUCTURE	1H NMR, δ	MS DATA	NAME
9		δ 6.9-8.0(7H,ArH), 4.03(3H,CH3), 3.6 (2H,CH2),2.39(3H,CH3)	neg.mode 390(M-1)	1-(4-methoxy-3-trifluoromethylbenzoyl)-2-methylindole-3-acetic acid
10		δ 7.8–6.9 (8H,ArH), 3.7(2H,CH2), 2.4(3H,CH3)	neg.mode 377(M-1)	1-(4-trifluoromethoxybenzoyl) -2-methylindole-3-acetic acid
11		δ 7-7.6(6H,ArH), 3.8(3H,CH3), 3.7 (2H,CH2), 2.38(3H,CH3)	neg.mode 392(M-1)	1-(3,5-dichlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid
12		δ 6.8-7.5(7H,ArH), 6.08(2H,CH2), 3.7(2H,CH2), 2.4(3H,CH3)	neg. mode 336(M-1), pos.mode 382(M+2Na)	1-(diperonyloylbenzoyl)-2-methylindole-3-acetic acid
13		δ6.6-7.7(9H,ArH), 3.7(2H,CH2), 2.4 (3H,CH3)	neg.mode 358(M-1), pos.mode 404(M+1)	1-(4-difluoromethoxybenzoyl) -2-methylindole-3-acetic acid
14		δ6.9-7.5 (7H,ArH), 3.7(2H,CH2), 2.4(3H,CH3)	neg.mode 372(M-1)	1-(2,2-difluoro-3,4-benzodioxolebenzoyl)-2-methylindole-3-acetic acid
15		δ6.9-7.7(8H,ArH), 3.7(2H,CH2),2.4(3H,CH 3)	neg.mode 327(M-1)	1-(5-chlorobenzoyl)-2-methylindole-3-acetic acid
16		δ6.9-7.7(8H,ArH), 3.7 (2H,CH2),2.39 (3H,CH3)	neg.mode 326(M-1)	1-(4-(trifluoromethylthio)benzoyl) -2-methylindole-3-acetic acid
17		δ7.1-7.5 (7H,ArH), 3.7(2H,CH2), 2.28(3H,CH3)	neg.mode 361 (M-1), pos.mode 408 (M+1)	1-(2,4-dichlorobenzoyl)-2-methylindole-3-acetic acid
18		δ6.9-8(8H,ArH), 3.7(2H,CH2), 2.4(3H,CH3)	neg.mode 360 (M-1), pos.mode 362(M+1)	1-(3-trifluoromethylbenzyl)-2-methylindole-3-acetic acid

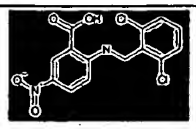
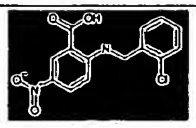
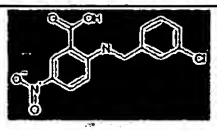
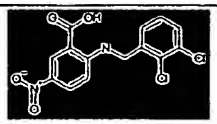
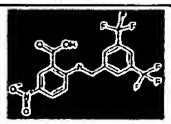
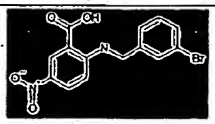
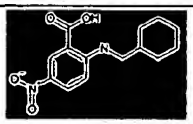
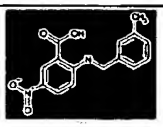
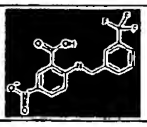
CMPD #	STRUCTURE	1H NMR, δ	MS DATA	NAME
19		(DMSO), δ 7.9–6.9(8H,ArH), 5.4(2H,CH2),3.62(2H,CH2),2.3(3H,CH3)	neg.mode 358 (M-1), pos.mode 359(M+1)	1-(4-bromobenzyl)-2-methylindole-3-acetic acid
20		δ 6.8-7.8 (7H,ArH), 3.7(2H,CH2), 2.4(3H,CH3), 1.4(9H,3CH3)	neg.mode 432(M-1)	1-(4-trifluoromethoxy)benzoyl-5-tertbutyl-2-methylindole-3-acetic acid

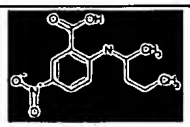
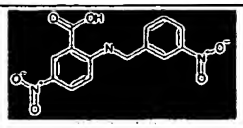
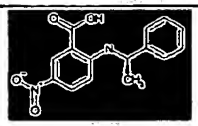
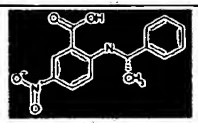
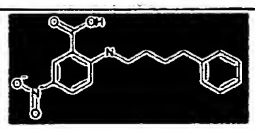
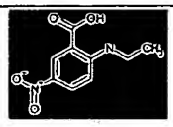
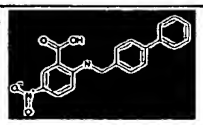
*The NMR data is reported for major peaks identified in the spectra, and as the skilled artisan recognizes, the NMR data is consistent with the indicated compounds.

Table 2
$A\beta_{42}$ Lowering Compounds*

CMPD #	STRUCTURE	1H NMR DATA (δ, ppm)	MS DATA	NAME
21		8.9 (d, 1H); 8.1 (dd, 1H); 7.1-7.3 (m, 5H); 6.5 (d, 1H); 3.3 (t, 2H, CH2); 2.7 (t, 2H, CH2); 2.0 (t, 2H, CH2).	299 (M-H)	5-nitro-2-(3-phenylpropylamino)benzoic acid
22		8.8 (d, 1H); 8.1 (dd, 1H); 7.1-7.3 (m, 5H); 6.6 (d, 1H); 4.5 (s, 2H, CH2).	271 (M-H)	2-benzylamino-5-nitrobenzoic acid
23		8.9 (d, 1H); 8.1 (dd, 1H); 7.3 (m, 3H); 6.5 (d, 1H); 4.5 (s, 2H, CH2).	339/341 (M-H)	2-(3,5-dichlorobenzylamino)-5-nitrobenzoic acid
24		8.9 (d, 1H); 8.2 (dd, 1H); 7.2-7.3 (m, 4H); 6.7 (d, 1H); 3.5 (t, 2H, CH2); 3.0 (t, 2H, CH2).	319 (M-H)	2-[2-(4-chlorophenyl)-ethylamino]-5-nitrobenzoic acid
25		8.9 (d, 1H); 8.4 (d, 1NH); 8.2 (dd, 1H); 7.1-7.3 (m, 5H); 6.5 (d, 1H); 3.6 (m, 1H, CH); 2.7 (t, 2H, CH2); 2.0 (m, 2H, CH2); 1.3 (d, 3H, CH3).	313 (M-H)	2-(1-methyl-3-phenylpropylamino)-5-nitrobenzoic acid

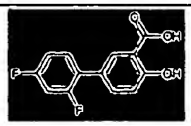
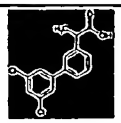
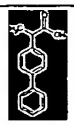
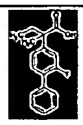
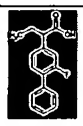
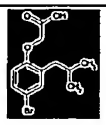
CMPD #	STRUCTURE	1H NMR DATA (δ, ppm)	MS DATA	NAME
26		8.9 (d, 1H); 8.2 (dd, 1H); 7.2-7.3 (m, 4H); 6.9 (d, 1H); 5.1 (t, 1H, CH); 2.9-3.1 (m, 2H, CH2); 2.6-2.7 (m, 1H, CH2); 1.9-2.1 (m, 1H, CH2).	297 (M-H)	2-(indan-1-ylamino)-5-nitrobenzoic acid
27		8.9 (d, 1H); 8.1 (dd, 1H); 7.4 (s, 1H); 6.9 (s, 2H); 6.7 (d, 1H); 4.5 (s, 2H, CH2); 2.3 (s, 6H, 2xCH3).	299 (M-H)	2-(3,5-dimethylbenzylamino)-5-nitrobenzoic acid
28		9.0 (d, 1H); 8.2 (dd, 1H); 7.3-7.4 (m, 4H); 6.6 (d, 1H); 4.6 (s, 2H, CH2).	306 (M-H)	2-(4-chlorobenzylamino)-5-nitrobenzoic acid
29		8.8 (d, 1H); 8.1 (dd, 1H); 6.8 (d, 2H); 6.7 (t, 1H); 6.5 (d, 1H); 4.5 (s, 2H, CH2).	307 (M-H)	2-(3,5-difluorobenzylamino)-5-nitrobenzoic acid
30		8.9 (d, 1H); 8.1 (dd, 1H); 6.6 (d, 1H); 6.4 (s, 2H); 6.3 (s, 1H); 4.4 (s, 2H, CH2); 3.7 (s, 6H, 2xOCH3).	331 (M-H)	2-(3,5-dimethoxybenzylamino)-5-nitrobenzoic acid
31		8.9 (m, 1H); 8.2 (m, 1H); 7.2-7.4 (m, 2H); 7.1 (m, 1H); 6.7 (m, 1H); 3.5 (m, 1H, CH2); 3.0 (m, 1H, CH2).	353/355 (M-H)	2-[2-(3,4-dichlorophenyl)-ethylamino]-5-nitrobenzoic acid
32		8.9 (d, 1H); 8.1 (dd, 1H); 7.4 (s, 1H); 7.2 (s, 2H); 6.5 (d, 1H); 4.6 (s, 2H, CH2).	339/341 (M-H)	2-(2,4-dichlorobenzylamino)-5-nitrobenzoic acid
33		8.9 (d, 1H); 8.1 (dd, 1H); 7.2-7.3 (m, 3H); 6.5 (d, 1H); 4.6 (s, 2H, CH2).	339/341 (M-H)	2-(2,5-dichlorobenzylamino)-5-nitrobenzoic acid
34		8.9 (d, 1H); 8.2 (dd, 1H); 7.8-7.9 (m, 2H); 7.7 (m, 1H); 7.5 (m, 2H); 7.4 (m, 2H); 6.7 (d, 1H); 4.9 (s, 2H, CH2).	321 (M-H)	2-[(naphthalen-1-ylmethyl)-amino]-5-nitrobenzoic acid
35		8.9 (d, 1H); 8.1 (dd, 1H); 7.4 (m, 2H); 7.1 (m, 1H); 6.5 (d, 1H); 4.4 (s, 2H, CH2).		2-(3,4-dichlorobenzylamino)-5-nitrobenzoic acid

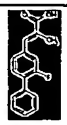
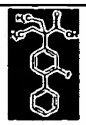
CMPD #	STRUCTURE	1H NMR DATA (δ, ppm)	MS DATA	NAME
36		8.8 (d, 1H); 8.2 (dd, 1H); 7.2-7.3 (m, 3H); 6.9 (d, 1H); 4.8 (s, 2H, CH2).	339/341 (M-H)	2-(2,6-dichlorobenzylamino)-5-nitrobenzoic acid
37		8.9 (d, 1H); 8.1 (dd, 1H); 7.3 (m, 1H); 7.1-7.2 (m, 3H); 6.5 (d, 1H); 4.6 (s, 2H, CH2).	305 (M-H)	2-(2-chlorobenzylamino)-5-nitrobenzoic acid
38		8.9 (d, 1H); 8.1 (dd, 1H); 7.1-7.3 (m, 4H); 6.5 (d, 1H); 4.5 (s, 2H, CH2).	305 (M-H)	2-(3-chlorobenzylamino)-5-nitrobenzoic acid
39		8.9 (m, 1H); 8.2 (m, 1H); 7.1-7.5 (m, 3H); 6.5 (m, 1H); 4.6 (s, 2H, CH2).	339/341 (M-H)	2-(2,3-dichlorobenzylamino)-5-nitrobenzoic acid
40		9.0 (m, 1H); 8.2 (m, 1H); 7.8 (m, 3H); 6.6 (m, 1H); 4.7 (m, 2H, CH2).	407 (M-H)	2-(3,5-bis-trifluoromethylbenzylamino)-5-nitrobenzoic acid
41		8.9 (d, 1H); 8.1 (dd, 1H); 7.4 (m, 2H); 7.1-7.3 (m, 2H); 6.5 (d, 1H); 4.5 (s, 2H, CH2).	350 (M-H)	2-(3-bromobenzylamino)-5-nitrobenzoic acid
42		8.9 (d, 1H); 8.5 (br. m, 1H); 8.2 (dd, 1H); 6.7 (d, 1H); 3.2 (t, 2H, CH2); 1.7-1.9 (m, 6H); 1.0-1.3 (m, 5H).	277 (M-H)	2-(cyclohexylmethylamino)-5-nitrobenzoic acid
43		8.9 (d, 1H); 8.1 (dd, 1H); 7.0-7.2 (m, 4H); 6.6 (d, 1H); 4.5 (s, 2H, CH2).	285 (M-H)	2-(3-methylbenzylamino)-5-nitrobenzoic acid
44		8.9 (d, 1H); 8.1 (dd, 1H); 7.5-7.6 (m, 4H); 6.6 (d, 1H); 4.6 (s, 2H, CH2).	339 (M-H)	2-(3-trifluoromethylbenzylamino)-5-nitrobenzoic acid

CMPD #	STRUCTURE	1H NMR DATA (δ, ppm)	MS DATA	NAME
45		8.9 (d, 1H); 8.4 (d, 1H); 8.2 (dd, 1H); 6.7 (d, 1H); 3.7 (m, 1H, CH); 1.3-1.7 (m, 7H); 1.0 (t, 3H, CH3).	251 (M-H)	2-(1-methyl-butylamino)-5-nitrobenzoic acid
46		8.9 (d, 1H); 8.1 (m, 3H); 7.5-7.6 (m, 2H); 6.5 (d, 1H); 4.6 (s, 2H, CH2).	316 (M-H)	2-(3-nitrobenzylamino)-5-nitrobenzoic acid
47		8.8 (d, 1H); 7.9 (dd, 1H); 7.1-7.3 (m, 5H); 6.4 (d, 1H); 4.6 (m, 1H, CH); 1.5 (d, 3H, CH3).	285 (M-H)	2-[(R)-1-phenylethylamino) -5-nitrobenzoic acid
48		8.9 (d, 1H); 8.0 (dd, 1H); 7.2-7.3 (m, 5H); 6.4 (d, 1H); 4.6 (m, 1H, CH); 1.6 (d, 3H, CH3).	285 (M-H)	2-[(S)-1-phenylethylamino) -5-nitrobenzoic acid
49		8.8 (d, 1H); 8.1 (dd, 1H); 7.1-7.3 (m, 5H); 6.6 (d, 1H); 3.3 (t, 2H, CH2); 2.6 (t, 2H, CH2); 1.7 (m, 4H, 2xCH2).	313 (M-H)	5-nitro-2-(4-phenylbutylamino) benzoic acid
50		8.8 (d, 1H); 8.2 (dd, 1H); 6.6 (d, 1H); 3.2 (m, 2H, CH2); 1.3 (t, 3H, CH3).	209 (M-H)	2-ethylamino-5-nitrobenzoic acid
51		8.9 (d, 1H); 8.1 (dd, 1H); 7.5-7.6 (m, 4H); 7.3-7.4 (m, 5H); 6.5 (d, 1H); 4.5 (s, 2H, CH2).	347 (M-H)	2-[(biphenyl-4-ylmethyl)-amino]-5-nitrobenzoic acid

* The skilled artisan understands that the compounds in table 2 that have an –N- group have the valences completed with a hydrogen; that is they are –NH- groups; the negative mode MS data reported; the NMR data is reported for major peaks identified in the spectra, and as the skilled artisan recognizes, the NMR data is consistent with the indicated compounds.

Table 3
$A\beta_{42}$ Lowering Compounds*

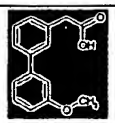
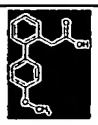
CMPD #	STRUCTURE	1H NMR DATA	MS DATA	NAME
52		Commercially Available		2',4'-Difluoro-4-hydroxy-biphenyl-3-carboxylic acid
53		δ 7.5 - 7.3 (m, 7H), 3.82 (q, J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H)	293 (M-1)	2-(3',5'-Dichloro-biphenyl-3-yl)-propionic acid
54		Commercially Available		Biphenyl-4-yl-acetic acid
55		δ 7.6 - 7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.1 (m, 2H), 3.70 (s, 2H)	229 (M-1) 230 (M+1)	(2-Fluoro-biphenyl-4-yl)-acetic acid
56		δ 7.6 - 7.5 (m, 4H), 7.5 - 7.3 (m, 5H), 3.80 (q, J = 7.2 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H)	225 (M-1)	2-Biphenyl-4-yl-propionic acid
57		δ 7.6 - 7.1 (m, 8H), 2.12 (m, 1H), 2.03 (m, 1H), 1.60 (s, 3H), 0.90 (app t, J = 7.4 Hz, 3H)	272 (M-1)	2-(2-Fluoro-biphenyl-4-yl)-2-methyl-butyric acid
58		δ 7.6 - 7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.1 (m, 2H), 3.51 (app t, J = 7.7 Hz, 1H), 2.12 (m, 1H), 1.88 (m, 1H), 0.96 (app t, J = 7.4 Hz, 3H)	258 ([M+1]); 214 (M-CO_2H)	2-(2-Fluoro-biphenyl-4-yl)-butyric acid
59		δ 7.3 - 7.2 (m, 2H), 6.61 (m, 1H), 4.66 (s, 2H), 2.50 (d, J = 7.1 Hz, 2H), 1.92 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H)	287 (M-1)	(4-Bromo-2-isobutyl-phenoxy)-acetic acid
60		(400 MHz) δ 7.56 - 7.51 (m, 2H), 7.47 - 7.34 (m, 4H), 7.28 - 7.19 (m, 2H), 1.64 (s, 6H)	214 (M-CO_2H)	2-(2-Fluoro-biphenyl-4-yl)-2-methyl-propionic acid

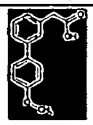
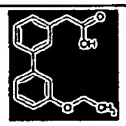
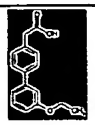
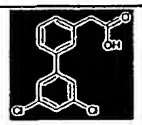
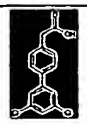
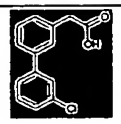
CMPD #	STRUCTURE	1H NMR DATA	MS DATA	NAME
61		δ 7.54 (m, 2H), 7.5 - 7.2 (m, 5H), 7.03 (m, 1H), 3.80 (q, *J* = 7.1 Hz, 1H), 1.56 (d, *J* = 7.2 Hz, 3H)	200 (M-CO2H)	2-(3'-Fluoro-biphenyl-4-yl)-propionic acid
62		δ 7.80 (m, 1H), 7.59 (m, 2H), 7.6 - 7.2 (m, 6H), 2.21 (d, *J* = 1.3 Hz, 3H)	256 (M+1) 255 (M-1)	(E)-3-(2-Fluoro-biphenyl-4-yl)-2-methyl-acrylic acid
63		δ 7.6 -7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.0 (m, 2H), 2.10 (m, 4H), 0.82 (app t, *J* = 7.4 Hz, 6H)	286 (M+1) 285 (M-1)	2-Ethyl-2-(2-fluoro-biphenyl-4-yl)-butyric acid

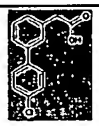
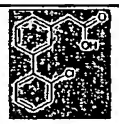
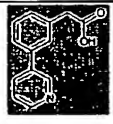
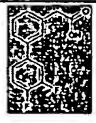
* The NMR data is reported for major peaks identified in the spectra, and as the skilled artisan recognizes, the NMR data is consistent with the indicated compounds.

Table 4

$A\beta_{42}$ Lowering Compounds

CMPD #	STRUCTURE	NAME
64		(2'-Methoxy-biphenyl-4-yl)-acetic acid
65		(3'-Methoxy-biphenyl-3-yl)-acetic acid
66		(3'-Methoxy-biphenyl-4-yl)-acetic acid
67		(4'-Methoxy-biphenyl-2-yl)-acetic acid

CMPD #	STRUCTURE	NAME
68		(4'-Methoxy-biphenyl-3-yl)-acetic acid
69		(4'-Methoxy-biphenyl-4-yl)-acetic acid
70		(3'-Ethoxy-biphenyl-3-yl)-acetic acid
71		(3'-Ethoxy-biphenyl-4-yl)-acetic acid
72		(3'-Fluoro-biphenyl-4-yl)-acetic acid
73		(4'-Fluoro-biphenyl-4-yl)-acetic acid
74		(3',5'-Dichloro-biphenyl-3-yl)-acetic acid
75		(3',5'-Dichloro-biphenyl-4-yl)-acetic acid
76		(3'-Chloro-biphenyl-3-yl)-acetic acid

CMPD #	STRUCTURE	NAME
77		(3'-Chloro-biphenyl-4-yl)-acetic acid
78		(4'-Chloro-biphenyl-3-yl)-acetic acid
79		(4'-Chloro-biphenyl-4-yl)-acetic acid
80		(2'-Chloro-biphenyl-3-yl)-acetic acid
81		(2'-Chloro-biphenyl-4-yl)-acetic acid
82		(4-Pyridin-3-yl-phenyl)-acetic acid
83		(3-Pyridin-3-yl-phenyl)-acetic acid
84		(3',4'-Difluoro-biphenyl-3-yl)-acetic acid
85		(3',4'-Difluoro-biphenyl-4-yl)-acetic acid

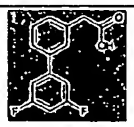
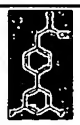
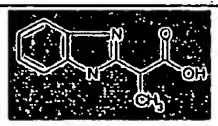
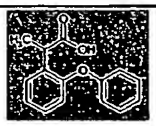
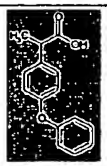
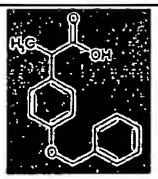
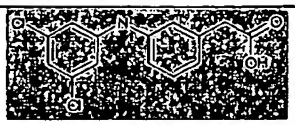
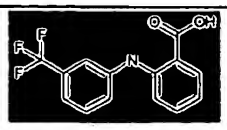
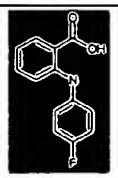
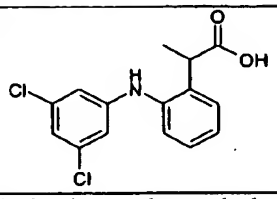
CMPD #	STRUCTURE	NAME
86		(3',5'-Difluoro-biphenyl-3-yl)-acetic acid
87		(3',5'-Difluoro-biphenyl-4-yl)-acetic acid
88		2-(1H-Benzoimidazol-2-yl)-propionic acid

Table 5

$A\beta_{42}$ Lowering Compounds*

CMPD #	STRUCTURE	1H NMR DATA	MS DATA	NAME
89		δ 7.4 - 6.8 (m, 9H), 4.11 (q, J = 7.2 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H)	241 (M-1)	2-(2-Phenoxy-phenyl)-propionic acid
90		δ 7.4 - 6.9 (m, 9H), 3.73 (q, J = 7.2 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H)	241 (M-1)	2-(4-Phenoxy-phenyl)-propionic acid
91		δ 7.5 - 7.2 (m, 7H), 6.94 (m, 2H), 5.05 (s, 2H), 3.70 (q, J = 7.2 Hz, 1H), 1.49 (d, J = 7.2 Hz, 3H)	255 (M-1)	2-(4-Benzyloxy-phenyl)-propionic acid
92		δ 3.62 (s, 2H), 6.83-7.32 (m, 7H)	295 (M+1)	[3-(3,5-Dichloro-phenylamino)-phenyl]-acetic acid

93		Commercially Available		2-(3-Trifluoromethyl-phenylamino)-benzoic acid
94		Commercially Available		2-(4-Fluoro-phenylamino)-benzoic acid
95				2-[2-(3,5-dichlorophenylamino)-phenyl]-propionic acid

* The skilled artisan understands that the compounds in Table 5 that have an –N- group have their valences completed with a hydrogen; that is they are –NH- groups; the NMR data is reported for major peaks identified in the spectra, and as the skilled artisan recognizes, the NMR data is consistent with the indicated compounds.

In one embodiment of the invention, a method for lowering $A\beta_{42}$ protein levels, in an individual in need of such treatment, is provided that includes the step of administering an effective amount of a compound of Formula I-IV as described above. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5.

While not wishing to be bound by theory, it is believed that the compound of Formula I-IV acts *in vivo* to treat and/or prevent Alzheimer's disease and MCI by lowering the amount of $A\beta_{42}$ that is present or would be present in the absence of such treatment. Amyloid β polypeptides are derived from amyloid precursor proteins (APPs). A variety of amyloid β polypeptides are known including $A\beta_{34}$, $A\beta_{37}$, $A\beta_{38}$, $A\beta_{39}$, and $A\beta_{40}$. Increased $A\beta_{42}$ levels are associated with Alzheimer's disease and MCI. Thus, by lowering the amounts of $A\beta_{42}$, a treatment is provided for combating Alzheimer's disease and/or MCI.

In another embodiment, the invention relates to a method of preventing Alzheimer's disease. According to this embodiment, a method for preventing Alzheimer's disease is provided which comprises administering, to an individual in need

of such treatment, a composition comprising a compound having Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5. The method of this embodiment is useful for preventing the symptoms of Alzheimer's disease, the onset of Alzheimer's disease, and/or the progression of the disease.

In another embodiment, the invention provides a method of treating a neurodegenerative disorder, by identifying a patient in need of such treatment, and administering to the patient a therapeutically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5. Administration of a compound of Formula I-IV for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, can provide an improvement or lessening in decline of cognitive function as characterized by cognition tests, biochemical disease marker progression, and/or plaque pathology. It is preferred that the lessening in decline in cognitive function is at least 25 % as compared to individuals treated with placebo, more preferably at least 40 %, and even more desirably at least 60 %. For example, an individual treated with placebo having probable mild-to-moderate Alzheimer's disease is expected to score approximately 5.5 points worse on the ADAS-cog test after a specified period of time of treatment (*e.g.*, 1 year) whereas an individual treated with the composition of this aspect of the invention for the same period of time will score approximately 2.2 points worse on the ADAS-cog scale with a 60% decrease in decline or 3.3 points worse with a 40% decrease in decline in cognitive function when treated with the composition for the same specified period of time. The pharmaceutical composition for use in the invention is formulated with one or more pharmaceutically acceptable excipients, salts, or carriers. The pharmaceutical composition for use in the invention is delivered orally, preferably in a tablet or capsule dosage form.

In yet another embodiment, the invention provides a method for prophylaxis against a neurodegenerative disorder, by identifying a patient in need of or desiring such treatment, and administering to the patient a prophylactically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5.

Administration of a compound of Formula I-IV for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, can delay the onset of the neurodegenerative disorder or slow the rate of onset of symptoms of the disorder. Patients having a predisposition to a neurodegenerative disorder or suspected of needing prophylaxis can be identified by any method known to the skilled artisan for diagnosis of such neurodegenerative disorders.

In still another embodiment, the invention provides a method of treating a disease characterized by abnormal amyloid precursor protein processing by (1) identifying a patient in need of such treatment, and (2) administering to the patient a therapeutically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5. Examples of biochemical disease markers include, for example, amyloid beta peptide (Aβ), Aβ_{42}, and tau.

In another embodiment, the invention provides a method of prophylaxis or delaying the onset of a disease (or one or more symptoms thereof) characterized by abnormal amyloid precursor protein processing, by identifying a patient in need of such treatment and administering to the patient a prophylactically effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5. Oral administration of the pharmaceutical composition for use in the method of this aspect the invention for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, prevents or delays the onset of the disease (or symptoms thereof) characterized by abnormal amyloid precursor protein processing.

In another embodiment, the invention provides a method of treating Alzheimer's disease comprising administering to a patient in need of such treatment, a pharmaceutical composition having one or more compounds of Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5. Oral administration of the pharmaceutical composition for use in the method of this aspect of the invention for at least 4 weeks, preferably at least 4 months, and more desirably at least 8 months, provides an improvement or lessening in decline of cognitive function as characterized by cognition tests, biochemical disease marker progression, and/or plaque pathology.

Desirably, the oral dose is provided in capsule or tablet form. According to this aspect of the invention, a patient in need of treatment is administered an Alzheimer's disease treating effective amount of a pharmaceutical composition having one or more compounds of Formula I-IV and one or more pharmaceutically acceptable salts, excipients and carriers. The method of this aspect of the invention involves identifying an individual likely to have mild-to-moderate Alzheimer's disease. An individual having probable mild-to-moderate Alzheimer's disease can be diagnosed by any method available to the ordinary artisan skilled in such diagnoses. For example, diagnosis can be according to DSM IV (TR) and/or meets NINCDS-ADRDA criteria for probable AD. According to this aspect of the invention, individuals with probable mild-to-moderate AD take an oral dose of a pharmaceutical composition for a specified period of time. Individuals undergoing such treatment are likely to see an improvement or lessening in decline of cognitive function, an improvement or lessening in decline in biochemical disease marker progression, and/or an improvement or lessening of decline in plaque pathology. A lessening in decline in cognitive function can be assessed using tests of cognitive function like the ADAS-cog. For example, an individual treated with placebo having probable mild-to-moderate Alzheimer's disease is expected to score approximately 5.5 points worse on the ADAS-cog test after a specified period of time of treatment (*e.g.*, 1 year) whereas an individual treated with the composition of this aspect of the invention for the same period of time will score approximately 2.2 points worse on the ADAS-cog scale with a 60% decrease in decline or 3.3 points worse with a 40% decrease in decline in cognitive function when treated with the composition for the same specified period of time. In a related aspect, the method involves identifying a patient having moderate-to-severe AD and administering to the patient an Alzheimer's disease treating effective amount of a compound of Formula I-IV.

In another embodiment, the invention provides a method of preventing the onset of Alzheimer's disease comprising administering to a patient in need of or desiring such treatment, a pharmaceutical composition having one or more compounds of Formula I-IV. Preferred compounds for use in this embodiment of the invention include those in Tables 1-5. Administration of the pharmaceutical composition for use in the method of this aspect of the invention for at least 4 weeks, preferably at least 4 months, and more

desirably at least 8 months, delays the onset of decline of cognitive function, biochemical disease marker progression, and/or plaque pathology. According to this embodiment, an individual desiring or needing preventative treatment against the onset of AD is administered a pharmaceutical composition having one or more compounds of Formula I-IV. The preventative treatment is preferably maintained as long as the individual continues to desire or need the treatment. Individuals needing or desiring preventative treatment against AD can be those having risk factors for developing AD. For example, risk factors for developing AD can be genetic factors or environmental factors. In one embodiment, the risk factor is age. Genetic risk factors can be assessed in a variety of ways, such as ascertaining the family medical history of the individual, or performing a genetic test to identify genes that confer a predisposition for developing AD. Additionally, risk factors can be assessed by monitoring genetic and biochemical markers. The method of this embodiment involves evaluating risk factors for cognitive decline. Evaluation of risk factors can include genetic testing for predisposing genes, alleles, and polymorphisms. Risk factors also refer to environmental factors like stroke, brain injury, age, and diet. Depending on the risk factor or factors associated with a particular patient a particular treatment regimen is selected for treating cognitive decline. For example, mutations in a Familial Alzheimer's disease gene are a risk factor. Another risk factor for cognitive decline is age. Head trauma is another risk factor for cognitive decline. Based on the patient's risk factors, a physician will prescribe a particular therapeutic treatment or prophylactic treatment suitable for the patient.

In still another embodiment, the invention provides a method of lowering $A\beta_{42}$ levels to a greater extent than inhibiting COX-1, COX-2, or a combination thereof. In particular, the method of this embodiment comprises administering to a patient in need of treatment an effective amount of one or more compounds of Formula I-IV. The method of this embodiment involves the lowering of $A\beta_{42}$ levels while not substantial affecting the activity of COX-1, COX-2, or both COX-1, and COX-2. Thus, the amount of the composition administered is effective for lowering $A\beta_{42}$ levels and does not substantially inhibit COX-1, COX-2, or both COX-1 and COX-2. For example, the effective amount can be above the ED50 (the dose therapeutically effective in 50% of the population) for $A\beta_{42}$ lowering, and below the ED50 for COX inhibition. Another example is a

sufficiently small amount of compound so that inhibition of at least one COX activity is negligible and $A\beta_{42}$ levels are reduced. The method of this embodiment can be used to treat and/or prevent Alzheimer's disease. The method of this embodiment can also be used to treat and/or prevent MCI and other neurodegenerative disorders.

According to a preferred embodiment, the invention provides a method of lowering $A\beta_{42}$ levels to a greater extent than inhibiting COX-1, COX-2, or a combination thereof. In particular, the method of this embodiment comprises administering, to a patient in need of treatment, an effective amount of one or more compounds of Formula I-IV, wherein the effective amount of compound is capable of lowering $A\beta_{42}$, while not substantially affecting or inhibiting the activity of at least one isoform of COX. Thus, the method of this embodiment involves the lowering of $A\beta_{42}$ levels while not substantially inhibiting the activity of COX-1, COX-2, or both COX-1 and COX-2. The method of this embodiment can be used to treat and/or prevent Alzheimer's disease, MCI, and/or other neurodegenerative disorders. In one aspect of this embodiment, the effective amount of compound having Formula I–IV reduces $A\beta_{42}$ levels or production of $A\beta_{42}$ by at least 1, 2, 5, 10, 15, 20, 25, 30, 40, or 50 or more percent while inhibiting COX-1, COX-2, or both COX-1 and COX-2 by less than 1, 2, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, or 90 percent. In a preferred aspect of this embodiment, the effective amount of compound according to Formula I-IV lowers $A\beta_{42}$ by at least 5 percent while not substantially inhibiting COX-1 , COX-2, or both COX-1 and COX-2 activity or levels. In another preferred aspect of this embodiment, the effective amount of the compound having Formula I-IV that is administered to an individual is such that it lowers $A\beta_{42}$ levels, and does not inhibit COX activity to a significant extent, *e.g.*, the amount administered is below the *in vivo* IC50 value for COX-1, COX-2 or both COX-1 and COX-2 and above the *in vivo* IC50 value for $A\beta_{42}$ lowering activity. As used in this context, IC50 refers to the amount of compound sufficient to inhibit COX activity by 50% (COX-1, COX-2, or both COX-1 and COX-2) or reduce $A\beta_{42}$ levels by 50%. An "effective amount" according to this preferred aspect of this embodiment, can also be viewed in terms of ED50 parameters, binding constants, dissociation constants, and other pharmacological parameters, *e.g.*, the amount administered is below the ED50 value for COX-1, COX-2 or both COX-1 and COX-2 and above the ED50 value for $A\beta_{42}$. It is

noted that the effective amount of the compound does not necessarily have to be above an IC50 or ED50 for $A\beta_{42}$ lowering and below the IC50 or ED50 for COX inhibition. That is, the "effective amount" can be at some intermediate value such that $A\beta_{42}$ levels are lowered to a greater extent than inhibition of COX-1, COX-2 or both COX-1 and COX-2.

Preferred compounds for use in each of the embodiments of the invention include 2-(2-fluoro-biphenyl-4-yl)-2-methyl-propionic acid, 2-ethyl-2-(2-fluoro-biphenyl-4-yl)-butyric acid, (4'-methoxy-biphenyl-3-yl)-acetic acid, (3',5'-dichloro-biphenyl-3-yl)-acetic acid, and 2-(3',5'-dichloro-biphenyl-3-yl)-propionic acid. Other preferred compounds for use in each of the embodiments of the invention include 1-(4-trifluoromethylbenzyl)-2-methylindole-3-acetic acid, 3,5-dichlorobenzoyl-2-methylindole-3-acetic acid, 1-(4-trifluoromethoxybenzoyl)-2-methylindole-3-acetic acid, 4-(trifluoromethylthio)benzoyl-2-methylindole-3-acetic acid, and 1-(4-trifluoromethoxy)benzoyl-5-tertbutyl-2-methylindole-3-acetic acid. Other preferred compounds for use in each of the embodiments of the invention include 2-(3,5-dimethylbenzylamino)-5-nitrobenzoic acid, 2-(3,4-dichlorobenzylamino)-5-nitrobenzoic acid, 2-(3-chlorobenzylamino)-5-nitrobenzoic acid, 2-(3,5-bis-trifluoromethylbenzylamino)-5-nitrobenzoic acid, and 2-(3-bromobenzylamino)-5-nitrobenzoic acid. Other preferred compounds for use in each of the embodiments of the invention include 2-(3-phenoxy-phenyl)-propionic acid, [3-(3,5-dichloro-phenylamino)-phenyl]-acetic acid, 2-(3-trifluoromethyl-phenylamino)-benzoic acid, and 2-[2-(3,5-dichlorophenylamino)-phenyl]-propionic acid.

An AD diagnosis can be made using any known method. Typically, AD is diagnosed using a combination of clinical and pathological assessments. For example, progression or severity of AD can be determined using Mini Mental State Examination (MMSE) as described by Mohs *et al. Int Psychogeriatr* 8:195-203 (1996); Alzheimer's Disease Assessment Scale-cognitive component (ADAS-cog) as described by Galasko *et al. Alzheimer Dis Assoc Disord*, 11 suppl 2:S33-9 (1997); the Alzheimer's Disease Cooperative Study Activities of Daily Living scale (ADCS-ADL) as described by McKhann *et al. Neurology* 34:939-944 (1984); and the NINCDS-ADRDA criteria as described by Folstein *et al. J. Psychiatr. Res.* 12:189-198 (1975). In addition, methods that allow for evaluating different regions of the brain and estimating plaque and tangle frequencies can be used. These methods are described by Braak *et al. Acta Neuropathol*

82:239-259 (1991); Khachaturian *Arch. Neuro.* 42:1097-1105 (1985); Mirra *et al.* (1991) *Neurology* 41:479-486; and Mirra *et al. Arch Pathol Lab Med* 117:132-144 (1993).

The invention further provides a combination therapy strategy for preventing Alzheimer's disease and MCI. According to this aspect of the invention, an individual in need of treatment is administered a compound having Formula I-IV (preferred compounds for use in this embodiment of the invention include those in Tables 1-5), and a compound selected from the group consisting of NSAIDs (non-steroidal anti-inflammatory drugs), COX-2 inhibitors (cyclooxygenase-2), β-secretase inhibitors, R-flurbiprofen, γ-secretase inhibitors, acetylcholine esterase inhibitors, and NMDA antagonists. Preferably the combination therapy involves treating the individual in need of treatment with a compound of Formula I-IV (*e.g.*, those in Tables 1-5) in combination with an acetylcholine esterase inhibitor or an NMDA receptor antagonist. Preferred acetylcholine esterase inhibitors for combination therapy are tacrine, donepezil, rivastigmine, and galantamine. Preferred NMDA receptor antagonists for combination therapy are memantine, adamantane, amantadine, an adamantane derivative, dextromethorphan, dextrorphan, dizocilpine, ibogaine, ketamine, and remacemide. The acetylcholine esterase inhibitor or NMDA receptor antagonists is preferably formulated in a combination dosage form with a compound of Formula I-IV (e.g., those in Tables 1-5).

The treatment regime used in the combination therapy can involve administration of a composition comprising the combination of active ingredients, the concomitant administration of separate compositions, each comprising at least one active ingredient. Furthermore, the administration of the active ingredients can be performed at different times and/or different routes. For example, a composition comprising at least one active ingredient can be administered in the morning, and a composition comprising at least one different active ingredient can be administered in the evening. Another example would involve the administration of a composition having at least one active ingredient orally while the second composition is administered intravenously.

While not wishing to be bound by theory, it is believed that the compounds of Formula I-IV are capable of slowing the rate of death of neurons. Accordingly, it is also believed that the compounds of Formula I-IV acts in vivo to treat and/or prevent

Alzheimer's disease and MCI by slowing the rate of death of neurons that is present or would be present in the absence of such treatment.

The skilled artisan readily recognizes that the invention includes the use of compounds of Formula I-IV, pharmaceutically acceptable salts, metabolites and prodrugs thereof in each of the described embodiments.

Definitions

As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; e.g., "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Even more preferably, it is a lower alkyl having 1 to 6 carbon atoms, and even more preferably 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, C-carboxy, O-carboxy, cyanato, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, and amino.

As used herein, the term "halo" refers to chloro, fluoro, bromo, and iodo.

As used herein, the term "hydro" refers to a hydrogen atom (-H group).

As used herein, the term "hydroxy" refers to an -OH group.

As used herein, the term "alkoxy" refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein. Lower alkoxy refers to -O-lower alkyl groups.

As used herein, the term "aryloxy" refers to both an -O-aryl and an -O-heteroaryl group, as defined herein.

As used herein, the term "mercapto" group refers to an -SH group.

As used herein, the term "alkylthio" group refers to both an S-alkyl and an -S-cycloalkyl group, as defined herein.

As used herein, the term "arylthio" group refers to both an -S-aryl and an -S-heteroaryl group, as defined herein.

As used herein, the term "carbonyl" group refers to a -C(=O)R" group, where R" is selected from the group consisting of hydro, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heterocyclic (bonded through a ring carbon), as defined herein.

As used herein, the term "aldehyde" group refers to a carbonyl group where R" is hydro.

As used herein, the term "cycloketone" refer to a cycloalkyl group in which one of the carbon atoms which form the ring has a "=O" bonded to it; i.e. one of the ring carbon atoms is a -C(=O)-group.

As used herein, the term "thiocarbonyl" group refers to a -C(=S)R" group, with R" as defined herein.

As used herein, the term "O-carboxy" group refers to a R"C(=O)O-group, with R" as defined herein.

As used herein, the term "C-carboxy" group refers to a -C(=O)OR" groups with R" as defined herein.

As used herein, the term "ester" is a C-carboxy group, as defined herein, wherein R" is any of the listed groups other than hydro.

As used herein, the term "C-carboxy salt" refers to a $-C(=O)O^- M^+$ group wherein M^+ is selected from the group consisting of lithium, sodium, magnesium, calcium, potassium, barium, iron, zinc and quaternary ammonium.

As used herein, the term "acetyl" group refers to a $-C(=O)CH_3$ group.

As used herein, the term "carboxyalkyl" refers to $-(CH_2)_rC(=O)OR"$ wherein r is 1-6 and R" is as defined above.

As used herein, the term "carboxyalkyl salt" refers to a $-(CH_2)_rC(=O)O^-M^+$ wherein M^+ is selected from the group consisting of lithium, sodium, potassium, calcium, magnesium, barium, iron, zinc and quaternary ammonium.

As used herein, the term "carboxylic acid" refers to a C-carboxy group in which R" is hydro.

As used herein, the term "haloalkyl" refers to an alkyl group substituted with 1 to 6 halo groups, preferably haloalkyl is a $-CX_3$ group wherein X is a halo group. The halo groups can be independently selected.

As used herein, the term "trihalomethanesulfonyl" refers to a $X_3 CS(=O)_2-$ group with X as defined above.

As used herein, the term "cyano" refers to a $-C\equiv N$ group.

As used herein, the term "cyanato" refers to a -CNO group.

As used herein, the term "isocyanato" refers to a -NCO group.

As used herein, the term "thiocyanato" refers to a -CNS group.

As used herein, the term "isothiocyanato" refers to a -NCS group.

As used herein, the term "sulfinyl" refers to a -S(=O)R" group, with R" as defined herein.

As used herein, the term "sulfonyl" refers to a $-S(=O)_2$ R" group, with R" as defined herein.

As used herein, the term "sulfonamido" refers to a $-S(=O)_2 NR^{17}R^{18}$, with R^{17} and R^{18} as defined herein.

As used herein, the term "trihalomethanesulfonamido" refers to a $X_3CS(=O)_2 NR^{17}$ -group with X and R^{17} as defined herein.

As used herein, the term "O-carbamyl" refers to a $-OC(=O)NR^{17} R^{18}$ group with R^{17} and R^{18} as defined herein.

As used herein, the term "N-carbamyl" refers to a $R^{18} OC(=O)NR^{17}-$ group, with R^{17} and R^{18} as defined herein.

As used herein, the term "O-thiocarbamyl" refers to a $-OC(=S)NR^{17} R^{18}$ group with R^{17} and R^{18} as defined herein.

As used herein, the term "N-thiocarbamyl" refers to a $R^{17}OC(=S)NR^{18}-$ group, with R^{17} and R^{18} as defined herein.

As used herein, the term "amino" refers to an $-NR^{17} R^{18}$ group, with R^{17} and R^{18} both being hydro.

As used herein, the term "C-amido" refers to a $-C(=O)NR^{17} R^{18}$ group with R^{17} and R^{18} as defined herein. An "N-amido" refers to a $R^{17} C(=O)NR^{18}-$ group with R^{17} and R^{18} as defined herein.

As used herein, the term "nitro" refers to a $-NO_2$ group.

As used herein, the term "quaternary ammonium" refers to a $-^{+}NR^{17}R^{18}R^{19}$ group wherein R^{17}, R^{18}, and R^{19} are independently selected from the group consisting of hydro and unsubstituted lower alkyl.

As used herein, the term "methylenedioxy" refers to a $-OCH_2O-$ group wherein the oxygen atoms are bonded to adjacent ring carbon atoms.

As used herein, the term "ethylenedioxy" refers to a $-OCH_2CH_2O-$ group wherein the oxygen atoms are bonded to adjacent ring carbon atoms.

As used herein, the term "cycloalkyl" refers to an all-carbon monocyclic or fused ring (i.e., rings which share an adjacent pair of carbon atoms) group wherein one or more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, adamantane, cyclohexadiene, cycloheptane and, cycloheptatriene. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heterocyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, carboxy, O-carbamyl, N-carbamyl, C-amido, N-amido, nitro, and amino.

As used herein, the term "heterocycle" refers to a mono or bicyclic ring that contains 4-12 atoms, at least one of which is selected from nitrogen, sulfur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a $-C(=O)-$, and a ring sulfur atom may be optionally oxidized to form S-oxide(s). Suitably "heterocycle" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. "Heterocycle" may be nitrogen or carbon linked. Example of "heterocycles" or "heterocyclic" rings include, but are not limited to, morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl, imidazolyl, imidazolidinyl, pyrazolidinyl, dioxanyl and dioxolanyl. "Heterocycle" can include heteroaryls when the pi-electron system of a heterocycle is completely conjugated.

As used herein, the term "aryl" refers to an all-carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups

are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from halo, trihalomethyl, alkyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, nitro, carbonyl, thiocarbonyl, C-carboxy, O-carboxy, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalo-methanesulfonamido, and amino.

As used herein, the term "heteroaryl" refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, quinazoline, purine and carbazole. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, halo, trihalomethyl, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, nitro, carbonyl, thiocarbonyl, sulfonamido, carboxy, sulfinyl, sulfonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, and amino.

As used herein, the term "preventing an increase in a symptom" refers to both not allowing a symptom to increase or worsen, as well as reducing the rate of increase in the symptom. For example, a symptom can be measured as the amount of particular disease marker, *i.e.*, a protein. In another example the symptom can be cognitive decline. Preventing an increase, according to the definition provided herein, means that the amount of symptom (*e.g.*, protein or cognitive decline) does not increase or that the rate at which it increases is reduced.

As used herein, the term "treating Alzheimer's disease" refers to a slowing of or a reversal of the progress of the disease. Treating Alzheimer's disease includes treating a symptom and/or reducing the symptoms of the disease.

As used herein, the term "preventing Alzheimer's disease" refers to a slowing of the disease or of the onset of the disease or the symptoms thereof. Preventing Alzheimer's disease can include stopping the onset of the disease or symptoms thereof.

As used herein, the term "$A\beta_{42}$ lowering" refers to the capability to reduce the amount of $A\beta_{42}$ present and/or being produced. Levels of $A\beta_{42}$ can be determined with an ELISA assay configured to detect $A\beta_{42}$. Methods of determining $A\beta_{42}$ levels are described in the examples and references cited therein.

As used herein, the term "unit dosage form" refers to a physically discrete unit, such as a capsule or tablet suitable as a unitary dosage for a human patient. Each unit contains a predetermined quantity of a compound of Formula I-IV, which was discovered or believed to produce the desired pharmacokinetic profile which yields the desired therapeutic effect. The dosage unit is composed of a compound of Formula I-IV in association with at least one pharmaceutically acceptable carrier, salt, excipient, or combination thereof.

As used herein, the term "dose" or "dosage" refers the amount of active ingredient that an individual takes or is administered at one time. For example, an 800 mg dose of a compound of Formula I-IV refers to, in the case of a twice-daily dosage regimen, a situation where the individual takes 800 mg of a compound of Formula I-IV twice a day, e.g., 800 mg in the morning and 800 mg in the evening. The 800 mg of a compound of Formula I-IV dose can be divided into two or more dosage units, *e.g.*, two 400 mg dosage units of a compound of Formula I-IV in tablet form or two 400 mg dosage units of a compound of Formula I-IV in capsule form.

"A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound.

"A pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein.

"A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound for use in the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and

organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrophosphates, dihydrophosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4 dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

Preparation of the compounds of the invention

Synthetic schemes and experimental descriptions for the compounds of Formula I-IV for use in the methods of the invention are given in Example 13 and Example 14 below. The general synthetic route for the compounds in Table 1 is described in Example 13 with specific exemplification for compound 20. The skilled artisan readily recognizes that the other compounds in Table 1 can be synthesized using a synthetic route analogous to that used for compound 20. The general synthetic route for the compounds in Table 2 is described in Example 13 with specific exemplification for compound 40. The skilled artisan readily recognizes that the other compounds in Table 2 can be synthesized using a synthetic route analogous to that used for compound 40. The compounds in Table 4 are available from Astatech (Princeton, NJ). The general synthetic route for the compounds in Tables 3 and 5 is described in Example 14 with specific exemplification for each compound. Compound 52 was obtained from MP Biomedical, Irvine, CA. Compounds 5, 54, 93, and 94 were obtained from Sigma-Aldrich, St. Louis, MO.

Dosages, formulations, and route of administration

The active compounds of this invention are typically administered in combination with a pharmaceutically acceptable carrier through any appropriate routes such as parenteral, oral, or topical administration, in a therapeutically (or prophylactically) effective amount according to the methods set forth above. A preferred route of administration for use in the invention is oral administration.

Generally, the toxicity profile and therapeutic efficacy of the therapeutic agents can be determined by standard pharmaceutical procedures in suitable cell models or animal models. As is known in the art, the LD50 represents the dose lethal to about 50% of a tested population. The ED50 is a parameter indicating the dose therapeutically effective in about 50% of a tested population. Both LD50 and ED50 can be determined in cell models and animal models. In addition, the IC50 may also be obtained in cell models and animal models, which stands for the circulating plasma concentration that is effective in achieving about 50% of the maximal inhibition of the symptoms of a disease or disorder. Such data may be used in designing a dosage range for clinical trials in humans. Typically, as will be apparent to skilled artisans, the dosage range for human use should be designed such that the range centers around the ED50 and/or IC50, but remains significantly below the LD50 dosage level, as determined from cell or animal models.

Typically, the compounds and compositions for use in the invention can be effective at an amount of from about 0.05 mg to about 4000 mg per day, preferably from about 0.1 mg to about 2000 mg per day. However, the amount can vary with the body weight of the patient treated and the state of disease conditions. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at predetermined intervals of time. The EC50 values discussed previously can desirably be used to identify specific pro-apoptotic compounds and compositions that can be used within predetermined, desirable dosage ranges.

In the case of combination therapy, a therapeutically effective amount of another therapeutic compound can be administered in a separate pharmaceutical composition, or alternatively included in the pharmaceutical composition according to the present invention. The pharmacology and toxicology of other therapeutic compositions are known in the art. See e.g., Physicians Desk Reference, Medical Economics, Montvale,

NJ; and The Merck Index, Merck & Co., Rahway, NJ. The therapeutically effective amounts and suitable unit dosage ranges of such compounds used in the art can be equally applicable in the present invention.

It should be understood that the dosage ranges set forth above are exemplary only and are not intended to limit the scope of this invention. The therapeutically effective amount for each active compound can vary with factors including but not limited to the activity of the compound used, stability of the active compound in the patient's body, the severity of the conditions to be alleviated, the total weight of the patient treated, the route of administration, the ease of absorption, distribution, and excretion of the active compound by the body, the age and sensitivity of the patient to be treated, and the like, as will be apparent to a skilled artisan. The amount of administration can also be adjusted as the various factors change over time.

The active compounds can also be administered parenterally in the form of solution or suspension, or in lyophilized form capable of conversion into a solution or suspension form before use. In such formulations, diluents or pharmaceutically acceptable carriers such as sterile water and physiological saline buffer can be used. Other conventional solvents, pH buffers, stabilizers, anti-bacterial agents, surfactants, and antioxidants can all be included. For example, useful components include sodium chloride, acetate, citrate or phosphate buffers, glycerin, dextrose, fixed oils, methyl parabens, polyethylene glycol, propylene glycol, sodium bisulfate, benzyl alcohol, ascorbic acid, and the like. The parenteral formulations can be stored in any conventional containers such as vials and ampules.

Routes of topical administration include nasal, bucal, mucosal, rectal, or vaginal applications. For topical administration, the active compounds can be formulated into lotions, creams, ointments, gels, powders, pastes, sprays, suspensions, drops and aerosols. Thus, one or more thickening agents, humectants, and stabilizing agents can be included in the formulations. Examples of such agents include, but are not limited to, polyethylene glycol, sorbitol, xanthan gum, petrolatum, beeswax, or mineral oil, lanolin, squalene, and the like. A special form of topical administration is delivery by a transdermal patch. Methods for preparing transdermal patches are disclosed, e.g., in

Brown, *et al., Annual Review of Medicine*, 39:221-229 (1988), which is incorporated herein by reference.

Subcutaneous implantation for sustained release of the active compounds may also be a suitable route of administration. This entails surgical procedures for implanting an active compound in any suitable formulation into a subcutaneous space, e.g., beneath the anterior abdominal wall. See, *e.g.*, Wilson *et al., J. Clin. Psych.* 45:242-247 (1984). Hydrogels can be used as a carrier for the sustained release of the active compounds. Hydrogels are generally known in the art. They are typically made by crosslinking high molecular weight biocompatible polymers into a network that swells in water to form a gel like material. Preferably, hydrogels are biodegradable or biosorbable. For purposes of this invention, hydrogels made of polyethylene glycols, collagen, or poly(glycolic-co-L-lactic acid) may be useful. See, *e.g.*, Phillips *et al., J. Pharmaceut. Sci.* 73:1718-1720 (1984).

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

Soft gelatin capsules can be prepared in which capsules contain a mixture of the active ingredient and vegetable oil or non-aqueous, water miscible materials such as, for example, polyethylene glycol and the like. Hard gelatin capsules may contain granules of the active ingredient in combination with a solid, pulverulent carrier, such as, for example, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin.

Tablets for oral use are typically prepared in the following manner, although other techniques may be employed. The solid substances are ground or sieved to a desired

particle size, and the binding agent is homogenized and suspended in a suitable solvent. The active ingredient and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension. The moistening typically causes the particles to aggregate slightly, and the resulting mass is gently pressed through a stainless steel sieve having a desired size. The layers of the mixture are then dried in controlled drying units for determined length of time to achieve a desired particle size and consistency. The granules of the dried mixture are gently sieved to remove any powder. To this mixture, disintegrating, anti-friction, and anti-adhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The operating parameters of the machine may be selected by the skilled artisan.

If the compound for use in the invention is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

If the compound for use in the invention is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium. These substituents may optionally be further substituted with a substituent selected from such groups.

EXAMPLES

Example 1: Tablets

Ingredient	Amount	Preferred Ranges
Compound of Formula I-IV	400 mg	+ 50% to -50%
Microcrystalline Cellulose	392 mg	+ 50% to -50%
Colloidal Silicon Dioxide	4 mg	+ 50% to -50%
Magnesium Stearate	4 mg	+ 50% to -50%

The tablets are prepared using art known procedures.

Example 2: Coated tablets

Ingredient	Amount	Preferred Ranges
Compound of Formula I-IV	400 mg	+ 50% to -50%
Microcrystalline Cellulose	392 mg	+ 50% to -50%
Colloidal Silicon Dioxide	4 mg	+ 50% to -50%
Magnesium Stearate	4 mg	+ 50% to -50%
Coated with Lactose monohydrate Hydroxyl propyl methyl cellulose Titanium dioxide Tracetin/glycerol triacetate Iron oxide		

The coated tablets are produced using art known procedures.

Example 3: Capsules

Ingredient	Amount	Preferred Ranges
Compound of Formula I-IV	400 mg	+ 50% to -50%

Microcrystalline Cellulose	392 mg	+ 50% to -50%
Colloidal Silicon Dioxide	4 mg	+ 50% to -50%
Magnesium Stearate	4 mg	+ 50% to -50%
Encapsulated in gelatin		

The capsules are produced using art known procedures.

Example 4: Tablets

Ingredient	**Amount**	**Preferred Ranges**
Compound of Formula I-IV	200 mg	+ 50% to -50%
Microcrystalline Cellulose	196 mg	+ 50% to -50%
Colloidal Silicon Dioxide	2 mg	+ 50% to -50%
Magnesium Stearate	2 mg	+ 50% to -50%

Example 5: Clinical Investigation of Compounds of Formula I-IV for Alzheimer's Disease

According to this example, a compound of Formula I-IV is examined for its actions in healthy subjects as well as subjects with mild to moderate Alzheimer's disease (AD). Evaluation of a compound of Formula I-IV for treating Alzheimer's is accomplished in a three-group parallel design; each group having 53 subjects for a total of 159 subjects. Subjects are treated with a compound of Formula I-IV or a matching placebo twice a day for forty-eight weeks.

Test AD subjects are selected based on the following criteria: Subjects (1) have a diagnosis of dementia according to the DSM IV (TR) and meets the NINCDS-ADRDA (McKhann *et al. Neurology* 34:939-944 (1984)) criteria for probable Alzheimer's disease, (2) have CT or MRI since onset of memory impairment demonstrating absence of clinically significant focal adhesion, (3) have MMSE (Mohs *et al. Int Psychogeriatr* 8:195-203 (1996)) score $\geq$15 and $\leq$26, (4) have a modified Hachinski Ischaemic score < 4, (5) age $\geq$ 45 years and living in the community at the time of enrollment, (6) signed patient informed consent form and willing/able to attend for duration of study, (7) read and understand English, six years of education or work history sufficient to exclude mental retardation. Subjects can have no unforeseen aspirin use other than for

cardioprotective therapy (*e.g.*, < 325 mg aspirin/day). Subjects taking acetylcholinesterase inhibitors may be enrolled as long as they have been on a stable treatment dose for at least three months. Subjects must have a reliable English speaking caregiver or informant to accompany the subject for clinic visits and be prepared to supervise medication.

Subjects are excluded according to the following criteria: treatment with memantine in past 4 weeks, current evidence or history in the last 2 years of epilepsy, focal brain lesion, head injury with loss of consciousness and or immediate confusion after the injury, or DSM-IV criteria for major psychiatric disorder including psychosis, major depression, bipolar disorder, alcohol or substance abuse, history of hypersensitivity to NSAIDS including COX-2 inhibitors, chronic use of NSAIDs at any dose more than 7 days per month for the two months prior to Study day 1, history of upper GI bleeding requiring treatment with the past 3 years, documented evidence of active gastric or duodenal ulcer disease within the past three months, history of NSAID-associated ulcers, history of, or evidence of active malignancy, except basal cell carcinoma and squamous cell carcinoma of the skin within the 24 months prior to entry, chronic or acute renal, hepatic, or metabolic disorder or any other condition, which in the Investigator's opinion, might preclude study participation, use of any investigational therapy within 30 days, or 5 half-lives whichever is longer, prior to screening, major surgery within 12 weeks prior to Study Day 1, patients with uncontrolled cardiac conditions (New York Heart Association Class III or IV), anticoagulant therapy such as warfarin with 12 weeks prior to randomization, treatment with any CYP2C9 inhibitor within a two-week period prior to randomization (examples include amiodarone/Cordarone®, fluconazole/Diflucan®, fluvoxamine/Luvox®, isoniazid/INH®, miconazole/Monistat®, phenylbutazone/Butazolidone®, probenicid/Benemid®, sulfamethoxazole/Gantanol®, sulfaphenazole, teniposide/Vumon®, trimethoprim/Bactrim®, zafirlukast/Accolate®; danshen (Salvia miltiorrhiza); Lycium barbarum.

Therapeutic Endpoints

The primary efficacy endpoint is the rate of decline in the ADAS-cog score based on either a slope calculated for each patient or on a Generalized Estimating Equations

(GEE) model. Secondary efficacy endpoints can include scores on the CIBIC+, NPI, ADCS-ADL, and CDR sum of boxes. Efficacy analyses for primary and secondary endpoints can include the baseline score as a covariate, and will also include a term for the stratification variable: use or nonuse of acetylcholinesterase inhibitor baseline. A modified intent to treat approach can be used in which all randomized subjects who receive any study treatment and have post-baseline efficacy assessment can be included in the intent to treat population using a last value carried forward approach. A per protocol analysis population can include all subjects in the intent to treat population who did not have any major protocol violations.

Subjects consist of men and women, ages 60-85, who are diagnosed with probable AD using the National Institute of Neurologic Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) test (McKhann *et al. Neurology* 34:939-944 (1984)) or have mild to moderate dementia as determined by the Mini-Mental State Examination (MMSE, Mohs *et al. Int Psychogeriatr* 8:195-203 (1996)). MMSE scores in the range of 15-25 indicate mild to moderate dementia. AD subjects have caregivers that can ensure compliance with medication regimens and with study visits and procedures.

Control subjects consist of men and women ages 60-80 that lack significant cognitive or functional complaints, or depression as determined by the Geriatric Depression Scale (GDS), and have MMSE scores in the range of 27-30. Control subjects have the same general requirements as AD subjects with the exception that caregivers are not required. Both AD subjects and control subjects have good general health, *i.e.*, subjects do not have serious or life-threatening comorbid conditions.

Subjects who have medically active major inflammatory comorbid condition(s) such as rheumatoid arthritis, or those who have peptic ulcer, gastro-intestinal bleeding, or intolerance of NSAIDs in the past are excluded from the study. Those who have contra-indications to lumbar puncture, such as severe lumbar spine degeneration, sepsis in the region of the lumbar spine, or a bleeding disorder are excluded from participation in the study. In addition, subjects who currently or recently use medications such as NSAIDs, prednisone, or immunosuppressive medications such as cyclophosphamide that could interfere with the study are excluded. Recently is defined as within one month before

undergoing the baseline visit (see next paragraph). Subjects undergoing acetylcholinsterase inhibitor (AChE-I) treatments for AD are not excluded if these subjects have been on stable doses for at least four weeks. Similarly, AD subjects taking antioxidants such as vitamin E, vitamin C, or Gingko biloba are not excluded if they have been on stable doses for at least four weeks. Subjects who use NSAIDs or aspirin on a regular basis are excluded. If needed, analgesics such as paracetamol (Tylenol) are provided during the fourteen-day study.

The study procedure consists of three in-clinic visits: an initial screening visit, a baseline visit, and a follow-up visit at fourteen days. During the screening visit, information needed to assess eligibility is obtained and MMSE is administered.

During the baseline visit, which takes place within two weeks of the screening visit, physical examinations and lumbar punctures are performed. Blood samples are drawn for laboratory tests such as APO-E genotyping and for plasma preparation. At this time, subjects or caregivers, in the case of AD subjects, are given a fourteen-day supply of study a compound of Formula I-IV along with instructions about timing of doses and potential adverse effects. (For AD subjects, caregivers are required to accompany subjects to each visit, and are responsible for monitoring and supervising administration of study a compound of Formula I-IV.) A calendar is provided on which times of medications and potential adverse symptoms are recorded.

The treatment regimen consists of a fourteen-day treatment with a compound of Formula I-IV in the form of capsules taken two times a day with meals. High and low study doses of a compound of Formula I-IV are used (*i.e.*, 800 mg and 400 mg.) A study dose of 800 mg consists of two 400 mg of a compound of Formula I-IV as tablets, while a study dose of 400 mg consists of one 400 mg of a compound of Formula I-IV (one therapeutic capsule (or tablet) and one placebo capsule (or tablet)). Compounds of Formula I-IV can be pre-packed into a day-by-day plastic medication dispenser.

During the follow-up visit, twelve or fourteen days after beginning treatment, vital signs and adverse side effects of study compounds of Formula I-IV are assessed. Surplus compounds of Formula I-IV can be returned and counted. In addition, lumbar punctures are performed and blood samples are drawn for laboratory tests and for plasma preparations.

Visits during which lumbar punctures are performed and blood samples are drawn are scheduled for mornings with overnight fasting to avoid obtaining post-prandial or hyperlipemic plasma samples, which can influence levels of Aβ40 and Aβ42. The following paragraph summarizes the biological markers that are analyzed from plasma and CSF samples.

Plasma and CSF biological markers Volume Assay Method Volume of CSF of Plasma Protein, glucose, 1 mL cells $A\beta_{40}$ ELISA 100 μL x 2 100 μL x 2 (in duplicate) $A\beta_{42}$ ELISA 100 μL x 2 100 μL x 2 (in duplicate) $A\beta_{38}$. Mass Spectrometry 1 mL Isoprostanes Gas Chromatography/ 2 mL Mass Spectrometry M-CSF ELISA 50 μL x 2 (in duplicate) MCP-1 ELISA 50 μL x 2 (in duplicate) Tau, ELISA 50 μL x 2 P-tau181 (in duplicate) 50 μL x 2 (in duplicate) Plasma levels of compounds of Formula I-IV by HPLC 1 mL. The assessment of these markers is within the skill of an ordinary artisan.

Patients having mild-to-moderate Alzheimer's disease undergoing the treatment regimen of this example with compounds of Formula I-IV in doses of about 10 mg to 1600 mg per day can experience a lessening in decline of cognitive function (as measured by ADAS-cog or CDR sum of boxes), plaque pathology, and/or biochemical disease marker progression.

Example 6: Treatment of Alzheimer's disease with a compound of Formula I-IV

The compounds of Formula I-IV can be administered twice daily as tablets containing 400 mg of active ingredient or as a capsule containing 400 mg of the active ingredient. A higher dose can be administered to the patient in need of such treatment which can involve the patient taking *e.g.*, a 800 mg dose of a compound of Formula I-IV in the morning and a 800 mg dose of a compound of Formula I-IV in the evening. Typically, for the treatment of mild-to-moderate Alzheimer's disease, an individual is diagnosed by a doctor as having the disease using a suitable combination of observations. One criterion indicating a likelihood of mild-to-moderate Alzheimer's disease is a score of about 15 to about 26 on the MMSE test. Another criteria indicating mild-to-moderate Alzheimer's disease is a decline in cognitive function. Compounds of Formula I-IV can also be administered in liquid dosage forms. The dosages can also be divided or

modified, and taken with or without food. For example, the 400 mg dose can be divided into two 200 mg tablets or capsules.

Depending on the stage of the disease, the compound (*i.e.*, Formula I-IV) can also be administered twice daily in liquid, capsule, or tablet dosage forms where the dose has various amounts (*i.e.*, 850 mg, 750 mg, 700 mg, 650 mg, 600 mg, 550 mg, 500 mg, 450 mg, 350 mg, 300 mg, 250 mg, 200 mg, 150 mg, and 100 mg). Again, the dosages can also be divided or modified, and taken with or without food. The doses can be taken during treatment with other medications for treating Alzheimer's disease or symptoms thereof. For example, the compound can be administered in the morning as a tablet containing 400 mg of active ingredient (*i.e.*, a compound of Formula I-IV) and an acetylcholine esterase inhibitor (*i.e.*, tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®)), and/or an NMDA antagonist (*i.e.*, memantine). It may be desirable to lower the amount of acetylcholine esterase inhibitor (and/or NMDA antagonist) and/or NSAID to avoid adverse side effects associated with higher doses of these compounds. Alternatively, the acetylcholine esterase inhibitor (and/or NMDA antagonist) and NSAID can be co-formulated into a single dosage form, *i.e.*, liquid, tablet, capsule, *etc.*

Patients having mild-to-moderate Alzheimer's disease undergoing the treatment regimen of this example with a compound of Formula I-IV in doses of about 20 mg to 1600 mg per day can experience a lessening in decline of cognitive function (as measured by the ADAS-cog or CDR sum of boxes), plaque pathology, and/or biochemical disease marker progression.

Example 7: Prevention of Alzheimer's Disease

Prior to the onset of symptoms of Alzheimer's disease or just at the very beginning stages of the disease, patients desiring prophylaxis against Alzheimer's disease can be treated with a compound of Formula I-IV. Those needing prophylaxis can be assessed by monitoring assayable disease markers, detection of genes conferring a predisposition to the disease, other risks factors such as age, diet, or other disease conditions associated with Alzheimer's. The patient can also be treated with a

combination of an NMDA antagonist and a compound of Formula I-IV to delay or prevent the onset of Alzheimer's disease or symptoms thereof.

The patient desiring prophylaxis against Alzheimer's disease or prophylaxis of a worsening of the symptoms of Alzheimer's disease can be treated with a compound of Formula I-IV in an amount sufficient to delay the onset or progression of symptoms of Alzheimer's disease. For example, a patient can be treated with 800 mg of a compound of Formula I-IV twice daily. Another preventive regimen involves administering to the patient 400 mg of a compound of Formula I-IV twice daily. These amounts of these active ingredients can be modified to lessen side-effects and/or produce the most therapeutic benefit. For example, 200 mg of a compound of Formula I-IV twice daily can be administered to reduce side-effects associated with the use of higher levels of the active ingredient. The preventive treatment can also be, *e.g.*, treatment on alternating days with a compound of Formula I-IV, or alternating weeks. Other preventive treatment regimens include, but are not limited to, treatment with a compound of Formula I-IV for 3 weeks out of every 4 weeks, or for several months followed by no treatment for a month and then treatment for several months in an alternating on/off schedule to reduce side-effects or toxicity problems.

Patients desiring or in need of prophylaxis against Alzheimer's disease undergoing the preventive regimen of this example with a compound of Formula I-IV in doses of about 20 mg to 1600 mg can decelerate or delay the onset of Alzheimer's disease or prevent the occurrence of Alzheimer's disease.

Example 8: Detection of Amyloid Beta with Biosource Elisa Kit (Camarillo, CA)

The present invention provides compositions and methods for lowering $A\beta_{42}$ levels. To test whether compounds and compositions are capable of modulating Aβ levels, a sandwich enzyme-linked immunosorbent assay (ELISA) is employed to measure secreted Aβ (Aβ42 and/or Aβ40) levels. In this example, H4 cells expressing wide type APP695 are seeded at 200,000 cells/ per well in 6 well plates, and incubated at 37 degree C with 5% CO_2 overnight. Cells are treated with 1.5 ml medium containing vehicle (DMSO) or a test compound at 1.25μM, 2.5μM, 5.0μM and 10.0μM (as well as other concentration if desirable) concentration for 24 hours or 48 hours. The supernatant

from treated cells is collected into eppendorf tubes and frozen at -80 degree C for future analysis.

The amyloid peptide standard is reconstituted and frozen samples are thawed. The samples and standards are diluted with appropriate diluents and the plate is washed 4 times with Working Wash Buffer and patted dry on a paper towel. 100 µL per well of peptide standards, controls, and dilutions of samples to be analyzed is added. The plate is incubated for 2 hours while shaking on an orbital plate shaker at RT. The plate is then washed 4 times with Working Wash Buffer and patted dry on a paper towel. Detection Antibody Solution is poured into a reservoir and 100 µL /well of Detection Antibody Solution is immediately added to the plate. The plate is incubated at RT for 2 hours while shaking and then washed four times with Working Wash Buffer and patted dry on a paper towel. Secondary Antibody Solution is then poured into a reservoir and 100 µL /well of Secondary Antibody Solution is immediately added to the plate. The plate is incubated at RT for 2 hours with shaking, washed 5 times with Working Wash Buffer, and patted dry on a paper towel.

100 µL of stabilized chromogen is added to each well and the liquid in the wells begins to turn blue. The plate is incubated for 30 minutes at room temperature and in the dark. 100 µL of stop solution is added to each well and the plate is tapped gently to mix resulting in a change of solution color from blue to yellow. The absorbance of each well is read at 450 nm having blanked the plate reader against a chromogen blank composed of 100 µL each of stabilized chromogen and stop solution. The plate is read within 2 hours of adding the stop solution. The absorbance of the standards is plotted against the standard concentration and the concentrations of unknown samples and controls are calculated.

Example 9: Detection of Amyloid Beta with Innogenetic Elisa Kit (Gent, Belgium)

The present invention provides compositions and methods for lowering $A\beta_{42}$ levels. To test whether compounds and compositions are capable of modulating Aβ levels, sandwich enzyme-linked immunosorbent assay (ELISA) is employed to measure secreted Aβ (Aβ42 and/or Aβ40) levels. In this example, H4 cells expressing wide type APP695 are seeded at 200,000 cells/ per well in 6 well plates, and incubated at

37 degree C with 5% CO_2 overnight. Cells are treated with 1.5 ml medium containing vehicle (DMSO) or a test compound at 1.25 μm, 2.5 μm, 5.0 μm and 10.0 μm concentration for 24 hours or 48 hours. The supernatant from treated cells is collected into eppendorf tubes and frozen at -80 degree C for future analysis.

130 μl per well of samples, standards, and blanks is added to a 96-well polypropylene plate. 200 μl of samples, standards, and blanks from the polypropylene plate is added to the antibody-coated plates. The strip-holder with the appropriate number of strips is applied to the antibody-coated plates and the strips are covered with an adhesive sealer. The plate is then incubated 3 hours at room temperature while shaking on an orbital plate shaker.

The first antibody solution is prepared with Conjugate Diluent 1 at 1:100 ratio. Each well of the antibody-coated plates is washed 5 times with 400 μl washing solution and 100 μl of the prepared first antibody solution is added to each well. The strips are applied to the plate, covered with an adhesive sealer, and the plate is incubated for 1 hour at room temperature while shaking on an orbital plate shaker.

The second antibody (conjugate 2) solution is prepared with Conjugate Diluent 2 at 1:100 ratio. Each well of the antibody-coated plates are washed 5 times with 400 μl washing solution and 100 μl of the prepared second antibody solution is added to each well. The strips are applied, covered with an adhesive sealer, and the plate is incubated 30 min at room temperature while shaking on an orbital plate shaker. Each well of the antibody-coated plates is then are washed for 5 times with 400 μl washing solution.

A substrate solution is prepared by diluting Substrate 100X with HRP Substrate Buffer. 100 μl of the prepared substrate solution is added to each well of the antibody-coated plate. The strips are applied, covered with an adhesive sealer, and the plate is incubated for 30 min at room temperature. 100 μl Stop Solution is then added to each well to stop the reaction. The strip-holder is carefully taped to ensure through mixing. The reader is blanked and the absorbance of the solution in the wells is read at 450 nm. The absorbance of the standards is plotted against the standard concentration and the concentration of samples is calculated using the standard curve.

Example 10: Neuroprotection Assay

The present invention provides compositions and methods for slowing the death

or decline of neurons. To test the ability of compositions of the present invention to protect against neurotoxicity, adult female Sprague Dawley rats are obtained and injected intraperitoneally with various doses of a composition of the present invention. At the same time, the test animals also receive a subcutaneous injection of MK-801 (0.5 mg/kg), which has been shown to consistently induce, in all treated rats, a fully developed neurotoxic reaction consisting of acute vacuole formation in the majority of pyramidal neurons in layers III and IV of the posterior cingulate and retrosplenial (PC/RS) cortices.

Control animals are administered the liquid which was used to dissolve the test agent and the same dosage of MK-801 (0.5 mg/kg sc). The animals are sacrificed four hours after treatment and the number of vacuolated PC/RS neurons are counted on each side of the brain, at a rostrocaudal level immediately posterior to where the corpus callosum ceases decussating across the midline (approximately 5.6 mm caudal to bregma). The toxic reaction approaches maximal severity at this level and shows very little variability between different animals.

Percentage reduction in neurotoxicity is calculated by dividing the mean number of vacuolated neurons in a given treatment group, by the mean number of vacuolated neurons in control animals that were treated with MK-801 but not the protective agent. The result is subtracted from one and multiplied by 100, to calculate a percentage. Linear regression analysis can be used to determine an ED50 (i.e., the dosage of a given compound that reduces the mean number of vacuolated neurons to 50% of the value in control animals), with the 25th and 75th percentiles defining the confidence limits.

Example 11: Treatment of Animals with a Compound to Determine the Compound's Effect on Levels of $A\beta_{42}$ and Alzheimer's Disease

To determine the effect of a composition of the present invention on levels of $A\beta_{42}$ and Alzheimer's Disease, an animal is treated with the compound and the levels of $A\beta_{42}$ in the brain are measured. Three month-old TG2576 mice that overexpress APP(695) with the "Swedish" mutation (APP695NL) are used. Mice overexpressing APP(695) with the "Swedish" mutation have high levels of soluble Aβ in the their brains and develop memory deficits and plaques with age, making them suitable for examining

the effect of compounds on levels of $A\beta_{42}$ and Alzheimer's Disease. "Test" TG25276 mice are treated with the compound and "control" TG25276 mice are not. The brain levels of SDS-soluble $A\beta_{40}$ and $A\beta_{42}$ for "test" mice are compared to "control" mice using ELISA. Test mice that have a reduction in $A\beta_{42}$ levels suggest that treatment with the compound could prevent amyloid pathology by decreasing the ratio of $A\beta_{42}$ to $A\beta_{40}$ in the brain.

Example 12: Treatment of Animals with a Compound to Determine the Compound's Effect on Memory and Alzheimer's Disease

The present invention provides compositions and methods for treating or preventing Alzheimer's Disease. To test the effect of compositions of the present invention on memory and Alzheimer's Disease, TG2576 mice that overexpress APP(695) with the "Swedish" mutation (APP695NL) are used. Mice overexpressing APP(695) with the "Swedish" mutation develop memory deficits and plaques with age, making them suitable for examining the effect of compounds on memory and Alzheimer's Disease. The test compound is administered daily for two weeks to test groups of the TG2576 mice in age groups of: 1) 4-5 months, 2) 6-11 months, 3) 12-18 months, and 4) 20-25 months. Groups of control TG2576 mice of corresponding ages are not administered the compound. Both control and test groups then have memory tested in a version of the Morris water maze (Morris, *J. Neurosci. Methods*, 11:47-60 (1984)) that is modified for mice. The water maze contains a metal circular pool of about 40 cm in height and 75 cm in diameter. The walls of the pool have fixed spatial orientation clues of distinct patterns or shelves containing objects. The pool is filled with room temperature water to a depth of 25cm and an escape platform is hidden 0.5 cm below the surface of the 25-cm-deep water at a fixed position in the center of one of the southwest quadrant of pool. The test and control mice are trained for 10 days in daily sessions consisting of four trials in which the mouse starts in a different quadrant of the pool for each trial. The mice are timed and given 60 seconds to find the escape platform in the pool. If the mice have not found the escape platform after 60 seconds, they are guided into it. The mice are then allowed to rest on the platform for 30 seconds and the amount of time it takes the mice to find the platform is recorded. Probe trials are run at the end

of the trials on the 4th, 7th, and 10th days of training, in which the platform is removed and the mice are allowed to search for the platform for 60 sec. The percentage of time spent in the quadrant where the platform was in previous trials is calculated.

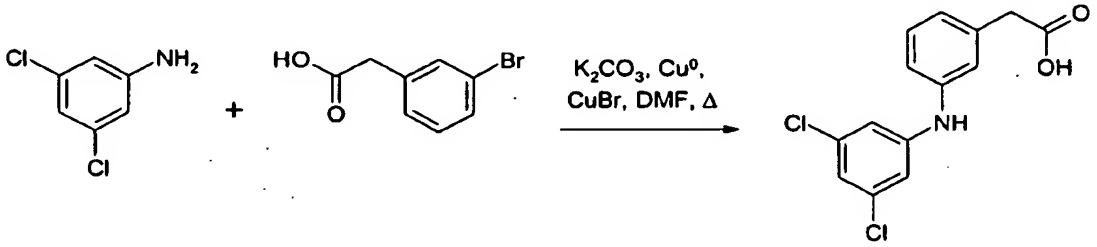
In training trials, the time it takes test group mice to reach the escape platform is compared to the time taken by control group mice of corresponding ages. In probe trials, the percentage of time spent by test group mice in the quadrant where the platform was in previous trials is compared to the percentage time spent by control mice. Quicker location of the escape platform in training trials and/or an increased percentage time spent in the previous quadrant of the maze during probe trials is indicative of spatial learning and memory. Because memory loss is a hallmark of Alzheimer's Disease, test mice that have better learning and memory when compared to control mice indicate that the compound may be effecting in treating or slowing Alzheimer's Disease and/or its symptoms.

Example 13: Synthesis of Compounds

General: Chemicals were purchased from standard commercial vendors and used as received unless otherwise noted. "Degassed" means reduced pressure then nitrogen gas for three cycles. Abbreviations are consistent with those in the ACS Style Guide., plus: satd (saturated), DCM (dichloromethane), pRPLC (preparative HPLC), "dry" glassware means oven/desiccator dried. Solvents were ACS grade unless otherwise noted. Analytical TLC plates (Silica Gel 60 F254, EM Science, Gibbstown, NJ, or Merck # 5715) were used to follow the course of reactions, and the MPLC system used for purifications was from Isco (Foxy Jr fraction collector, UA-6 detector), using Isco silica gel flash columns (10 or 40 g). ^{1}H NMR spectra in $CDCl_3$, CD_3OD, and/or d6-DMSO were recorded on either a Varian Mercury 400 MHz or Brucker ARX-300 MHz instrument and chemical shifts are expressed in parts per million (ppm, δ) relative to TMS as the internal standard. Mass spectra were obtained on a Thermo Finnigan LCQ-Deca (injection volume 5 uL, XTerra MS-C_{18} 3.5 μm 2.1 x 50mm column, XTerra MS-C_{18} 5 μm 2.1 x 20mm guard column), ESI source, analytical HPLC was performed on an HP1050 (injection volume 5 μl, XTerra RP-C_{18} 5 μm 4.6 x 250 mm column, with an XTerra MS-C_{18} 5 μm 2.1 x 20mm guard column), and preparative HPLC was performed

on an Agilent 1100 Prep-LC with various columns and conditions depending on the compound. GCMS was performed on either an Agilent Technology 6890N or Shimadzu QP5000/17A instrument. Yields are unoptimized.

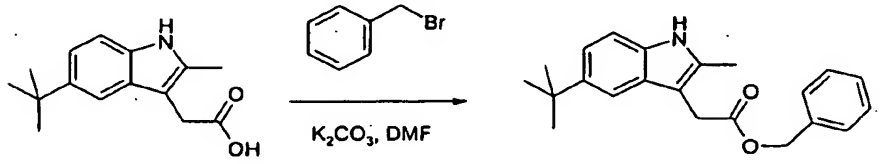
Synthetic Scheme for Compound 92

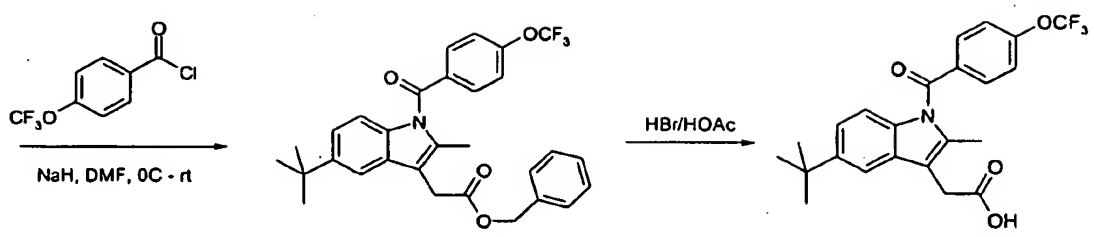


Experimental Section for Synthesis of Compound 92

[3-(3,5-dichloro-phenylamino)-phenyl]acetic acid: In a 100 mL round-bottomed flask, 3,5-dichloroaniline (3.84 g, 23.72 mmol), 3-bromophenyl acetic acid (3.00 g, 13.95 mmol), K_2CO_3 (granular, anhydrous; 3.29 g, 23.72 mmol), copper powder (50 mg, catalytic amount), and DMF (20 mL) were added and refluxed for 15 min. At this point copper bromide (3 x 50 mg, catalytic amount) was added over 30 min. Finally the reaction was refluxed for 4 h, then cooled to room temperature and poured into water (50 mL) and made acidic (pH 3) with HCl (12N) and extracted with EtOAc (2 x 25 mL). The organic layer was evaporated under vacuum to yield 928 mg (23 % yield) of crude product. This material was further purified by preparatory HPLC to yield 150 mg (4 % yield) of a light gray solid final product. TLC (10% MeOH in DCM) Rf = 0.23. HPLC RT = 6.39; MS, 295 (M+1) 250, 252, 294, 296. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 2H), 6.83-7.32 (m, 7H).

Synthetic Scheme for Compound 20





Experimental Section for the Synthesis of Compound 20

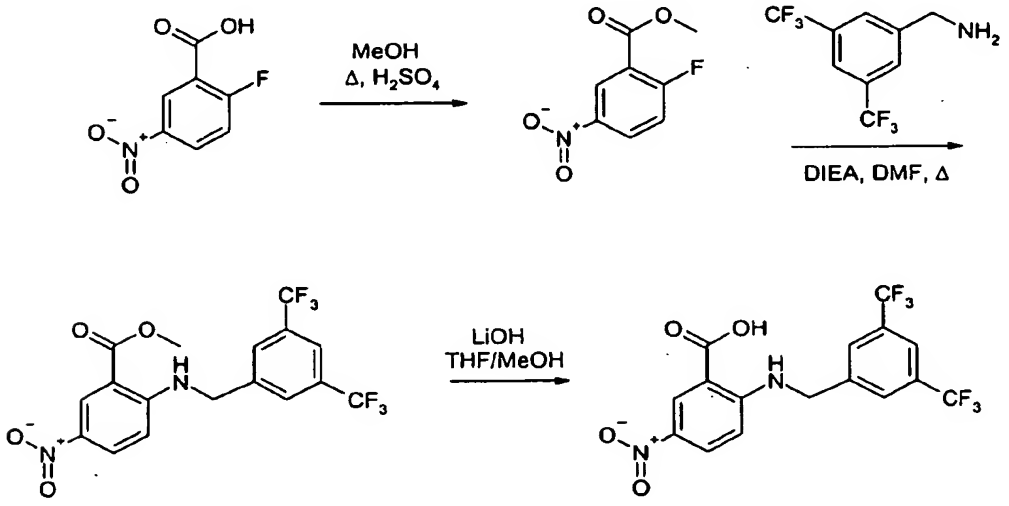
5-t-butyl-2-methylindole-3-benzylacetate: A mixture of 0.5 g (2 mmol) of 5-t-butyl-2-methylindole-3-acetic acid, 0.28 g (2 mmol) of potassium carbonate and 0.24 g (2 mmol) of benzyl bromide in 20 mL of DMF was stirred overnight at RT. The reaction mixture was diluted with 30 ml of water and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic solutions are washed with water (2 x 20 mL), dried (Na_2SO_4) filtered, and the solvent removed *in vacuo*. The crude product was purified by MPLC (5% - 10% EtOAc/hexanes as eluent) and obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (s, 1H), 7.2-7.5 (8H), 5.1 (s, 2H), 3.7 (s, 2H), 2.4 (s, 3H), 1.4 (s, 9H); GCMS: 9.1 min RT, 335 mass.

1-(p-trifluoromethoxybenzoyl)-5-t-butyl-2-methyl-3-benzylacetate: To a solution of 0.67 g (1.99 mmol) of 5-t-butyl-2-methylindole-3-benzylacetate in dry DMF (20 mL) was added 0.095 g of NaH (2.39 mmol; 60% dispersion in mineral oil) at 0 °C, under nitrogen. The reaction mixture was stirred at 0 °C for 20 min, and then 0.49 g (2.19 mmol) of 4-trifluoromethoxybenzoyl chloride in 2 mL DMF was added dropwise. The reaction mixture was then stirred at ambient temperature for 20 h, diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic solutions were washed with water (2 x 25 mL), dried (Na_2SO_4), and filtered, and the solvent removed *in vacuo*. The crude product was purified by MPLC (5% - 20% EtOAc/hexanes as eluent) and obtained as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.9-7.8 (12H), 5.1 (s, 2H), 3.7 (s, 2H), 2.4 (s, 3H), 1.4 (s, 9H); GCMS: 11 min RT, 523 mass.

1-(p-trifluoromethoxybenzoyl)-5-t-butyl-2-methyl-3-acetic acid: A mixture of 0.22 g (0.42 mmol) of 1-(p-trifluoromethoxybenzoyl)-5-t-butyl-2-methyl-3-benzylacetate and 12 mL of 33 wt% HBr/HOAc was stirred at 45-50° C for 5 h. After cooling, the reaction mixture was poured into a beaker with 70 mL of water. A white precipitate

appeared, and was allowed to sit for 2 h, then the precipitate was filtered off and washed with water, and then dried *in vacuo*. The purification of the crude product was done by preparative HPLC, and the product was obtained as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.8-7.9 (7H), 3.7 (s, 2H), 2.4 (s, 3H), 1.4 (s, 9H); ESI (positive mode) 479 (M+2Na), ESI (negative mode) 432 (M-H).

Synthetic Scheme for Compound 40



Experimental Section for Synthesis of Compound 40

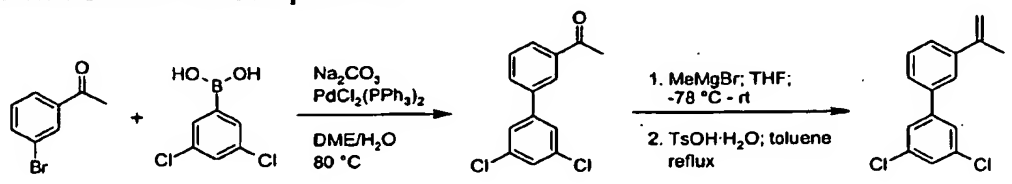
2-fluoro-5-nitrobenzoic acid methyl ester: To a solution of 3.3 g (17.8 mmol) 2-fluoro-5-nitrobenzoic acid in 10 mL (246 mmol) MeOH in a 100 mL round-bottom flask with a magnetic stir bar, was added 0.25 mL (catalytic) concentrated sulfuric acid. The flask was fitted with a reflux condenser and heating mantle, and the clear yellow solution stirred at 80°C for 7 h. After cooling, the solution was extracted from water 2 x EtOAc, the organic layers combined and washed once each with 1M HCl, saturated $NaHCO_3$, and brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to a pale yellow oil that solidified upon standing. ^{1}H (300 MHz, $CDCl_3$) δ 8.9 (m, 1H), 8.5 (m, 1H), 7.4 (t, 1H), 4.0 (s, 3H). GCMS: RT = 4.36 min, MW = 199.

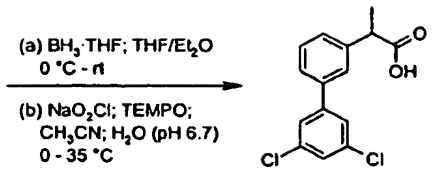
2-(3,5-bis-trifluoromethylbenzylamino)-5-nitrobenzoic acid methyl ester: To a solution of 0.198 g (1.01 mmol) of 2-fluoro-5-nitrobenzoic acid methyl ester in 8.0 mL anhydrous DMF in a 25 mL round-bottomed flask with a magnetic stir bar, was added 0.695 g (2.86 mmol) 3,5-bis(trifluoromethyl)benzylamine and 0.27 mL (1.55 mmol) DIEA. The flask was fitted with a reflux condenser and heating mantle, and the yellow suspension was stirred at 80 °C for 4 h. The yellow suspension turned clear within 15 min. After cooling to room temperature, the solution was extracted from water 2 x EtOAc, the organic layers combined and washed once each with water, dilute HCl, saturated $NaHCO_3$, and brine, dried over sodium sulfate, filtered and concentrated in vacuo to a pale yellow solid. This material was purified by MPLC using EtOAc/hexanes (10% - 50% gradient), the main product eluted as a single peak on GCMS: RT = 9.8 min, MW = 422 MW. ^{1}H NMR (300 MHz, $CDCl_3$ δ 9.1 (s, 1H), 8.3 (s, 1H), 8.2 (d, 1H), 7.8 (s, 1H), 7.7 (s, 2H), 6.5 (d, 1H), 4.7 (d, 2H), 4.0 (s, 3H).

2-(3,5-bis-trifluoromethylbenzylamino)-5-nitrobenzoic acid: To a solution of 0.360 g (0.90 mmol) of 2-(3,5-bis-trifluoromethylbenzylamino)-5-nitrobenzoic acid methyl ester in 10.0 mL of a 3:1 mixture of THF/MeOH in a 100 mL round-bottom flask with a magnetic stir bar, was added 2.7 mL (2.7 mmol) 1.0M LiOH, to give a clear yellow solution that darkened over time. The flask was loosely capped with a rubber septum, and the solution stirred at room temperature for 8 h. The solution was extracted from 1M HCl with 2 x EtOAc, the organic layers combined and washed once each with 1M HCl and brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to a yellow solid. HPLC RT = 16.9 min; LCMS (negative mode), 407 MW (M-H); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 8.9 (s, 1H), 8.2 (dd, 1H), 7.8 (s, 1H), 7.7 (s, 2H), 6.5 (d, 1H), 4.7 (s, 2H).

Example 14: Synthesis of Compounds

Synthetic Scheme for Compound 53





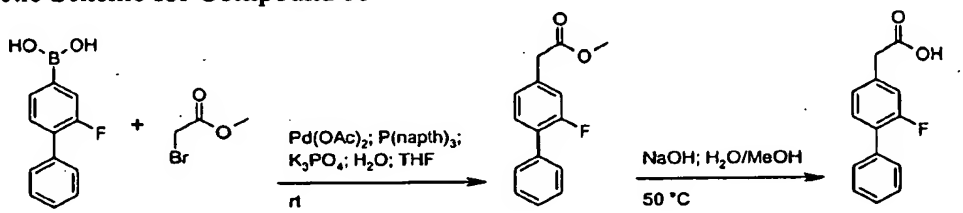
Experimental Section for Synthesis of Compound 53

Water (20 mL) and DME (100 mL) were added to a flask containing m-bromoacetophenone (3.995 g; 20.1 mmol), 3,5-dichlorobenzeneboronic acid (4.215 g; 22.1 mmol), sodium carbonate (3.195 g; 30.1 mmol) and bis(triphenylphosphine)palladium(II) chloride (423 mg; 0.603 mmol). The mixture was degassed then heated under a nitrogen atmosphere for 45 h; whereupon the organic volatiles were removed on a rotary evaporator. Water (20 mL) was added and the crude product extracted into a mixture of EtOAc (40 mL) and ether (50 mL). The organic portion was washed with 1 M NaOH (2 x 20 mL), 1 M HCl (2 x 20 mL) and satd NaCl (2 x 25 mL); then dried over $MgSO_4$, filtered and concentrated to 5.82 g of a white solid. This crude material was recrystallized from hot hexanes (300 mL) yielding 2.92 g (55%) of 1-(3',5'-dichloro-biphenyl-3-yl)-ethanone as white crystals. R_f 0.22 (10:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (m, 1H), 7.98 (m, 1H), 7.74 (m, 1H), 7.57 (m, 1H), 7.49 (m, 2H), 7.38 (m, 1H).

Using dry glassware, methylmagnesium bromide (3.0 M in ether; 1.50 mL; 4.5 mmol) was added dropwise via syringe to a soln at -78 °C of the above ketone (1.000 g; 3.77 mmol) in anhydrous THF (20 mL). After 2.6 h at -78 °C and brief ambient warming, the flask was put into a rt water bath then quenched after 10 min with 1 M HCl (10 mL). The organic volatiles were removed on a rotary evaporator and the crude product extracted into toluene (15 mL). The organic portion was washed with 1 M HCl (1 x 10 mL) and satd NaCl (2 x 10 mL), then dried over $MgSO_4$ and filtered into a round-bottomed flask yielding crude 2-(3',5'-dichloro-biphenyl-3-yl)-propan-2-ol. $TsOH·H_2O$ (36 mg; 0.19 mmol) was added and the rxn was heated at reflux overnight, then concentrated on a rotary evaporator and purified by MPLC (10 g SiO_2 with hexanes as eluant) yielding 600 mg of 3,5-dichloro-3'-isopropenyl-biphenyl as a clear, colorless liquid (60% over two steps). R_f 0.52 (hexanes); GC-MS (t_R = 7.0 min; *m/z* 262 $[M]^+$).

Using dry glassware, BH_3·THF (1.5 M in THF/ether) was added dropwise to a 0 °C soln of the above styrene (600 mg; 2.28 mmol) in anhydrous THF. After 1.2 h at 0 °C, potassium phosphate buffer (0.67 M; pH 6.7) was added (cautiously at first). The organic volatiles were removed on a rotary evaporator then acetonitrile (15 mL), TEMPO (25 mg; 0.16 mmol) and sodium chlorite (tech = 80wt%; 1.097 g; 9.7 mmol) were added. The rxn was heated at 35 °C for 40 h with vigorous stirring, then cooled in an ice-water bath and carefully quenched with sodium sulfite (428 mg; 3.4 mmol) and the pH adjusted to ca. 9, stirred for a short while then acidified with concentrated HCl. Water was added and the crude product extracted into DCM. The soln was dried over $MgSO_4$, filtered and concentrated. 2-(3',5'-Dichloro-biphenyl-3-yl)-propionic acid was partially purified by MPLC (SiO_2/0 - 50% EtOAc in hexanes) and further purified by pRPLC (149 mg; 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 - 7.3 (m, 7H), 3.82 (q, J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H); HPLC (t_R = 16.9 min); LC-MS (t_R = 8.9 min; *m/z* 293([M-1]$^-$; ESI$^-$).

Synthetic Scheme for Compound 55

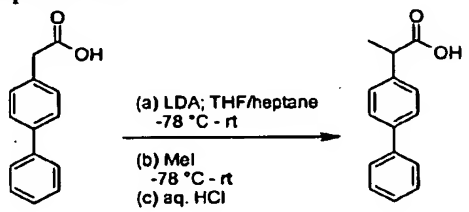


Experimental Section for Synthesis of Compound 55

THF (40 mL), water (0.38 mL; 21.1 mmol) and methyl bromoacetate (1.0 mL; 10.5 mmol) were added to a mixture of $Pd(OAc)_2$ (67.2 mg; 0.299 mmol), tri(1-naphyl)phosphine (369 mg; 0.895 mmol), potassium phosphate (10.614 g; 50.0 mmol) and 2-fluoro-biphenyl-4-boronic acid (2.593 g; 12.0 mmol). The rxn was degassed then vigorously stirred at rt. After 24 h, EtOAc (125 mL) was added and the mixture washed with water (3 x 25 mL) and satd NaCl (3 x 25 mL); then dried over $MgSO_4$, filtered, adsorbed onto silica then purified by MPLC (120 g SiO_2/0 - 20% EtOAc in hexanes yielding 1.527 g of impure (2-fluoro-biphenyl-4-yl)-acetic acid methyl ester (ca. 82wt% by GC-MS; ca. 49% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 - 7.3 (m, 6H), 7.2 - 7.0 (m, 2H), 3.73 (s, 3H), 3.67 (s, 2H); GC-MS (t_R = 6.3 min; *m/z* 244([M$^+$]).

The above methyl ester (127 mg; 0.520 mmol), 1 M NaOH (1 mL) and MeOH (1 mL) were heated at 50 °C. After 16.5 h the reaction was acidified with 1 M HCl (5 mL), the organic volatiles removed on a rotary evaporator then the product extracted into EtOAc (5 mL). The organic portion was washed with 1 M HCl (3 x 2 mL) and satd NaCl (2 x 2 mL), dried over $MgSO_4$, filtered then purified by MPLC (12 g SiO_2/EtOAc in hexanes gradient) yielding (2-fluoro-biphenyl-4-yl)-acetic acid as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 - 7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.1 (m, 2H), 3.70 (s, 2H); HPLC (t_R = 11.7 min); LC-MS (t_R = 5.3 min; *m/z* 229 ([M-1]$^-$; ESI-)); GC-MS (t_R = 6.9 min; *m/z* 230 ([M$^+$]).

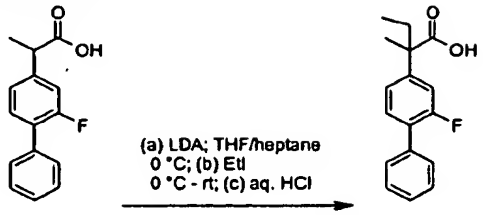
Synthetic Scheme for Compound 56



Experimental Section for Synthesis of Compound 56

Using dry glassware, LDA (2 M in THF/heptane; 2.0 mL; 4.0 mmol) was added to a -78 °C soln of biphenyl-4-yl-acetic acid (387 mg; 1.82 mmol) in anhydrous THF (4 mL). THF (15 mL) was added to the resulting ppt and the rxn warmed to rt to try to dissolve the ppt. The rxn was cooled to -78 °C, neat CH_3I (227 μL; 3.64 mmol) was added then the rxn stirred at rt. After 16 h the rxn was quenched with 1 M HCl (5 mL), the organic volatiles removed on a rotary evaporator then the product extracted into EtOAc (5 mL). The org. soln was washed with 1 M HCl (3 x 2 mL) and satd NaCl (2 x 2 mL), dried over $MgSO_4$, filtered then purified by MPLC (12 g SiO_2/EtOAc in hexanes gradient) yielding 95 mg of 2-biphenyl-4-yl-propionic acid as a solid (23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 - 7.5 (m, 4H), 7.5 - 7.3 (m, 5H), 3.80 (q, J = 7.2 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H); HPLC (t_R = 12.4 min); LC-MS (t_R = 5.45 min; *m/z* 225 ([M-1]$^-$; (ESI-)).

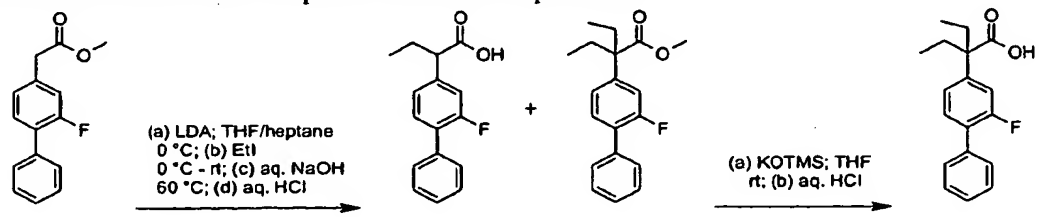
Synthetic Scheme for Compound 57



Experimental Section for Synthesis of Compound 57

LDA (2 M in THF/heptane; 0.75 mL; 1.5 mmol) was added to a 0 °C soln of 2-(2-fluoro-biphenyl-4-yl)-propionic acid (150 mg; 0.614 mmol) in anhydrous THF (5 mL). Neat iodoethane (99 μL; 1.2 mmol) was added after 10 min and the rxn was allowed to warm to rt. After 20 h, the rxn was concentrated on a rotary evaporator, 1 M HCl (3 mL) was added then the product extracted into EtOAc (5 mL). The organic portion was washed with 1 M HCl (2 mL) and hexanes (2 mL) was added to facilitate separation of the layers. The soln was further washed with satd NaCl (3 mL), filtered through a plug of silica then purified by MPLC (12 g SiO_2/0 - 30% EtOAc in hexanes) yielding 137 mg of 2-(2-fluoro-biphenyl-4-yl)-2-methyl-butyric acid as a tan, crystalline solid (82%). R_f 0.35 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 - 7.1 (m, 8H), 2.12 (m, 1H), 2.03 (m, 1H), 1.60 (s, 3H), 0.90 (app t, J = 7.4 Hz, 3H); HPLC (t_R = 14.4 min); LC-MS (t_R = 6.1 min; *m/z* 272 ([M-1).

Synthetic Scheme for Compound 58 and Compound 63



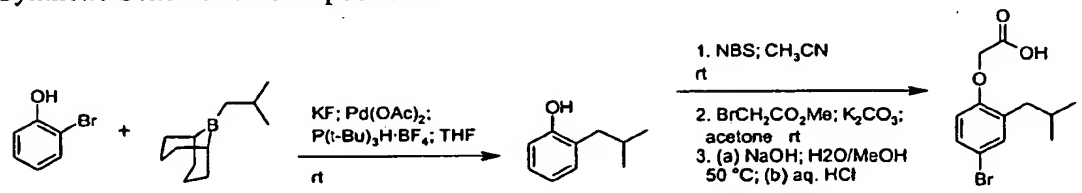
Experimental Section for Synthesis of Compound 58 and Compound 63

(2-Fluoro-biphenyl-4-yl)-acetic acid methyl ester (ca. 82 wt %; 150 mg; 0.504 mmol) was alkylated as for 2-(2-fluoro-biphenyl-4-yl)-2-methyl-butyric acid (compound 57) using THF (5 mL), LDA (2 M in THF/heptane; 0.75 mL; 1.5 mmol) and iodoethane (99 μL; 1.2 mmol). After 19 h, 1 M NaOH (2.0 mL; 2.0 mmol) was added and the rxn

heated at 60 °C for 7.5 h; whereupon the organic volatiles were removed on a rotary evaporator, 2 M HCl (3 mL) was added and the products extracted into EtOAc (5 mL). This was washed with 1 M HCl (2 x 2 mL) and satd NaCl (2 x 2 mL), dried over $MgSO_4$, filtered through a plug of silica then purified by MPLC (12 g SiO_2/0 - 30% EtOAc in hexanes) yielding 60 mg (46%) of 2-(2-fluoro-biphenyl-4-yl)-butyric acid as a light orange waxy solid and 64 mg (42%) of 2-ethyl-2-(2-fluoro-biphenyl-4-yl)- butyric acid methyl ester as a pale yellow viscous liquid. 2-(2-Fluoro-biphenyl-4-yl)-butyric acid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 - 7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.1 (m, 2H), 3.51 (app t, J = 7.7 Hz, 1H), 2.12 (m, 1H), 1.88 (m, 1H), 0.96 (app t, J = 7.4 Hz, 3H); GC-MS (t_R = 7.3 min; *m/z* 258 ([M^+]); HPLC (t_R = 13.7 min); LC-MS (t_R = 6.9 min; *m/z* 214 ([M-CO_2H]$^-$). 2-Ethyl-2-(2-fluoro-biphenyl-4-yl)- butyric acid methyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 -7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.0 (m, 2H), 3.69 (s, 3H), 2.07 (m, 4H), 0.77 (app t, J = 7.4 Hz, 6H).

Potassium silanolate (90% tech; 588 mg; 4.1 mmol) was added to a soln of 2-ethyl-2-(2-fluoro-biphenyl-4-yl)-butyric acid methyl ester (62 mg; 0.21 mmol) in anhydrous THF (4.2 mL). After 2 days at rt the rxn was determined to be incomplete by TLC and the temperature was increased to 60 °C. After 15 days at 60 °C the rxn was cooled to rt, quenched with 2 M HCl (2.5 mL) then the organic volatiles were removed on a rotary evaporator. The product was extracted into EtOAc (5 mL), washed with satd NaCl (1 x 4 mL), dried over $MgSO_4$, filtered through a plug of silica then conc on a rotary evaporator. Pure 2-ethyl-2-(2-fluoro-biphenyl-4-yl)-butyric acid (47 mg; 80%) was obtained as a white crystalline solid after MPLC (12 g SiO_2/0 - 40% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 -7.5 (m, 2H), 7.5 - 7.3 (m, 4H), 7.2 - 7.0 (m, 2H), 2.10 (m, 4H), 0.82 (app t, J = 7.4 Hz, 6H); GC-MS (t_R = 8.2 min; *m/z* 286 ([M^+]); HPLC (t_R = 16.7 min); LC-MS (t_R = 8.7 min; *m/z* 285 (M-1).

Synthetic Scheme for Compound 59



Experimental Section for Synthesis of Compound 59

In dry glassware, isobutylene gas was bubbled for 10 min into a soln of 9-BBN-H (0.5 M in THF; 30.0 mL; 15.0 mmol). The rxn was degassed. 2-Bromophenol (1.50 mL; 12.9 mmol), KF (2.256 g; 38.8 mmol), $Pd(OAc)_2$ (87.1 mg; 0.388 mmol) and P(t-Bu)$_3$H·BF_4 (113 mg; 0.388 mmol) were added and the rxn again degassed. After 23 h the rxn was concentrated on a rotary evaporator. Ether (50 mL) was added and washed with water (1 x 15 mL), 1 M HCl (2 x 15 mL), 1 M NaOH (3 x 15 mL) and satd NaCl (2 x 15 mL). The soln was dried over $MgSO_4$, filtered, adsorbed onto silica then purified by MPLC (40 g SiO_2/1 - 10% EtOAc in hexanes) yielding 1.836 g of 2-isobutyl-phenol as a pale yellow liquid that was 81 wt % pure by GC-MS (77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1 - 7.0 (m, 2H), 6.86 (m, 1H), 6.76 (m, 1H), 4.58 (s, 1H), 2.48 (d, J = 7.2 Hz, 2H), 1.93 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H); GC-MS (t_R = 2.8 min; *m/z* 150 ([M^+]).

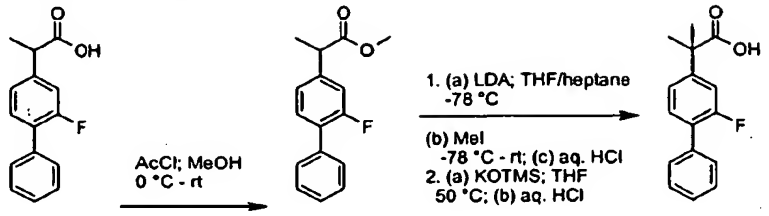
Solid NBS (1.771 g; 9.95 mmol) was added in one portion to a soln of the above phenol (1.83 g; 9.89 mmol) in acetonitrile at rt. After 50 min the rxn mixture was adsorbed onto silica then purified by MPLC (40 g SiO_2/0 - 10% EtOAc in hexanes) yielding 2.21 g of 4-bromo-2-isobutyl-phenol as a tan liquid (92wt% pure by GC-MS; 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 - 7.1 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H),4.60 (s, 1H), 2.44 (d, J = 7.2 Hz, 2H), 1.92 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H).

Methyl bromoacetate (1.25 mL; 13.2 mmol) was added to a suspension of potassium carbonate (1.84 g; 13.3 mmol) and the above bromophenol (2.03 g; 8.2 mmol) in acetone (15 mL). After 44 h at rt the rxn was conc on a rotary evaporator. Ether (20 mL) was added and washed with water (1 x 8 mL then 1 x 5 mL), 1 M HCl (1 x 5 mL) and satd NaCl (2 x 5 mL). After drying over $MgSO_4$ and filtration, the crude product was adsorbed onto silica then purified by MPLC (40 g SiO_2/0 - 100% EtOAc in hexanes) yielding pure (4-bromo-2-isobutyl-phenoxy)-acetic acid methyl ester as a light tan liquid (2.444 g; 100%). GC-MS (t_R = 5.9 min; *m/z* 300/302 ([M^+]).

The above methyl ester (155 mg; 0.515 mmol) was saponified in an analogous manner as for (2-fluoro-biphenyl-4-yl)-acetic acid methyl ester (compound 55) and purified by pRPLC yielding (4-bromo-2-isobutyl-phenoxy)-acetic acid as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 - 7.2 (m, 2H), 6.61 (m, 1H), 4.66 (s, 2H), 2.50 (d, J =

7.1 Hz, 2H), 1.92 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H); HPLC (t_R = 14.3 min); LC-MS (t_R = 7.2 min; *m/z* 287 ([M-1]$^-$).

Synthetic Scheme for Compound 60



Experimental Section for Synthesis of Compound 60

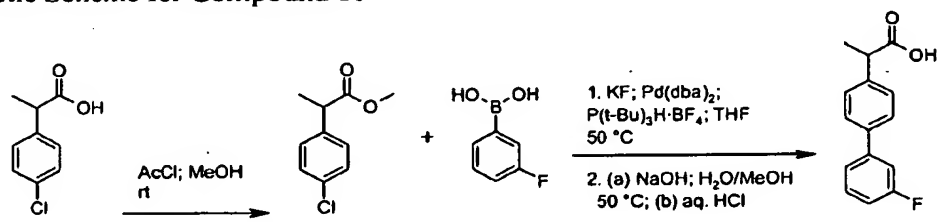
Neat acetyl chloride (0.90 mL; 12.7 mmol) was added to dry methanol (25 mL) at 0°C. After warming to rt over 10 min, solid (R)-flurbiprofen (6.109 g; 25.0 mmol) was added. The reaction was concentrated on a rotary evaporator after 26 h. The resulting oil was dissolved in ethyl acetate (40 mL) then washed with 1 M NaOH (1 x 10 mL), 1 M HCl (1 x 10 mL) and saturated NaCl (1 x 10 mL). The organic portion was dried ($MgSO_4$), filtered and concentrated to give 6.3 g of (R)-2-(2-fluoro-biphenyl-4-yl)-propionic acid methyl ester as a clear, colorless liquid (98%). ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.55 - 7.48 (m, 2H), 7.48 - 7.30 (m, 4H), 7.18 - 7.05 (m, 2H), 3.76 (q, J = 7.1 Hz, 1H), 3.70 (s, 3H), 1.54 (d, J = 7.1 Hz, 3H); GCMS (t_R = 6.4 min, *m/z* 258 (M^+)).

A solution of (R)-2-(2-fluoro-biphenyl-4-yl)-propionic acid methyl ester (1.943 g; 7.52 mmol) in dry THF (8 mL) was added over ca. 4 min via syringe to a solution at -78 °C of LDA (4.5 mL of 2.0M; 9.0 mmol) in heptane/THF. THF (2 mL) was used to quantitatively transfer the ester and THF (20 mL) was added to the resulting precipitate. The reaction was warmed in a rt water bath to dissolve the precipitate, then neat iodomethane (0.50 mL; 8.0 mmol) was added. After 3.0 h the reaction was quenched with 1M HCl (10 mL) then the organic volatiles were removed on a rotary evaporator. The product was extracted into ethyl acetate (25 mL) and the organic portion was washed with 1M HCl (3 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL), saturated NaCl (2 x 10 mL), then dried ($MgSO_4$), filtered and concentrated. 2-(2-Fluoro-biphenyl-4-yl)-2-methyl-propionic acid methyl ester was purified by MPLC (40 g SiO_2 column, 0 - 10% EtOAc/hexanes) to a clear, colorless oil which solidified to a waxy solid. This material

was 12.2:1 product:starting material (93 wt% pure) by GC-MS and was used as is for the following reaction. ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.58 - 7.49 (m, 2H), 7.49 - 7.31 (m, 4H), 7.20 - 7.08 (m, 2H), 3.70 (s, 3H), 1.61 (s, 6H); GCMS (t_R = 6.6 min, *m/z* 272 (M^+)).

Solid KOTMS (6.34 g; 44.5 mmol) was added to a solution of the above methyl ester (1.211 g; 4.13 mmol) in dry THF (25 mL). The reaction was put under an atmosphere of nitrogen then heated at 50 °C for 20 h, then cooled to 0 °C and acidified with concentrated HCl (5 mL). After concentration on a rotary evaporator, EtOAc (25 mL) was added and washed with water (1 x 15 mL then 2 x 5 mL) and saturated NaCl (2 x 8 mL). The solution was dried ($MgSO_4$), filtered, concentrated then purified by pRPLC yielding 153 mg of 2-(2-fluoro-biphenyl-4-yl)-2-methyl-propionic acid as a white solid (14% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.56 - 7.51 (m, 2H), 7.47 - 7.34 (m, 4H), 7.28 - 7.19 (m, 2H), 1.64 (s, 6H); HPLC (t_R = 13.5 min); LC-MS (t_R = 6.9 min; *m/z* 214 ([M-CO_2H]$^-$).

Synthetic Scheme for Compound 61



Experimental Section for Synthesis of Compound 61

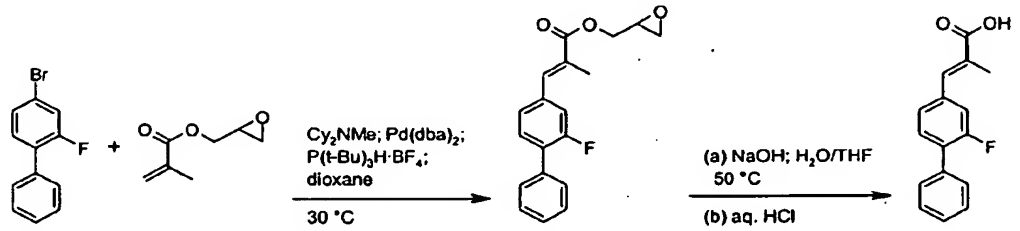
2-(4-Chloro-phenyl)-propionic acid methyl ester was synthesized in an analogous manner as for (R)-2-(2-fluoro-biphenyl-4-yl)-propionic acid methyl ester (compound 60) from 2-(4-chloro-phenyl)-propionic acid (4.000 g; 21.7 mmol), acetyl chloride (1.5 mL; 21.1 mmol) and methanol (35 mL) yielding 3.986 g of a light yellow liquid after MPLC purification (120 g SiO_2/EtOAc in hexanes gradient). GC-MS (t_R = 3.5 min; *m/z* 198 ([M^+]).

Anhydrous THF (2.0 mL) was added to a vial containing the above ester (149 mg; 0.735 mmol), 3-fluorophenylboronic acid (115 mg; 0.822 mmol), potassium fluoride (141 mg; 2.43 mmol), $Pd(dba)_2$ (14.5 mg; 0.0252 mmol) and P(t-Bu)$_3$H·BF_4 (8.9 mg; 0.031 mmol). The rxn was degassed then heated at 50 °C for 44 h. Hexanes (2 mL) was added

and the rxn filtered through a plug of silica and washed through with EtOAc. Concentration on a rotary evaporator yielded crude 2-(3'-fluoro-biphenyl-4-yl)-propionic acid methyl ester, which was used as is in the next rxn. R_f 0.26 (10:1 hexanes:EtOAc).

The above methyl ester was saponified in an analogous manner as for (2-fluoro-biphenyl-4-yl)-acetic acid methyl ester (compound 55) and purified by MPLC (12 g SiO_2/0 - 50% EtOAc in hexanes) yielding 2-(3'-fluoro-biphenyl-4-yl)-propionic acid as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.5 - 7.2 (m, 5H), 7.03 (m, 1H), 3.80 (q, J = 7.1 Hz, 1H), 1.56 (d, J = 7.2 Hz, 3H); HPLC (t_R = 14.6 min); LC-MS (t_R = 6.9 min; m/z 200 ([M-CO_2H]$^-$; ESI-)).

Synthetic Scheme for Compound 62



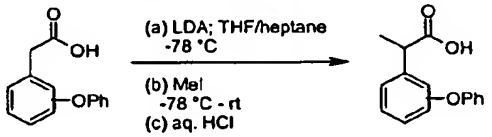
Experimental Section for Synthesis of Compound 62

Anhydrous dioxane (2.0 mL) then dicyclohexyl-methyl-amine (0.48 mL; 2.2 mmol) then 2-methyl-acrylic acid oxiranylmethyl ester (0.55 mL; 4.0 mmol) were added to the solid reagents 4-bromo-2-fluoro-biphenyl (504 mg; 2.01 mmol), $Pd(dba)_2$ (35 mg; 0.061 mmol) and $P(t\text{-}Bu)_3H{\cdot}BF_4$ (17.2 mg; 0.0593 mmol). The rxn was degassed then heated at 30 °C. After 94 h, EtOAc (6 mL) was added, the rxn filtered through a plug of silica, concentrated on a rotary evaporator then purified by MPLC (40 g SiO_2/0 - 20% EtOAc in hexanes) yielding 605 mg of (E)-3-(2-fluoro-biphenyl-4-yl)-2-methyl-acrylic acid oxiranylmethyl ester as a white solid (97%). R_f 0.23 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 1H), 7.58 (m, 2H), 7.6 - 7.2 (m, 6H), 4.59 (dd, J = 3.0, 12.3 Hz, 1H), 4.07 (dd, J = 6.4, 12.3 Hz, 1H), 3.33 (m, 1H), 2.91 (m, 1H), 2.72 (dd, J = 2.6, 4.8 Hz, 1H), 2.20 (d, J = 1.4 Hz, 3H); GC-MS (t_R = 9.2 min; m/z 312 ([M^+]).

The above ester (413 mg; 1.32 mmol), 1 M NaOH (3.0 mL) and THF (3.0 mL) were reacted at 50 °C for 70 h; whereupon the rxn was concentrated on a rotary

evaporator, acidified with 1 M HCl (4 mL) then extracted with EtOAc. The organic portion was washed with satd NaCl, dried over $MgSO_4$, filtered through a plug of silica then purified by MPLC (40 g SiO_2/0 - 50% EtOAc in hexanes) yielding 83 mg of (E)-3-(2-fluoro-biphenyl-4-yl)-2-methyl-acrylic acid as a white crystalline solid (24%). R_f 0.23 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 1H), 7.59 (m, 2H), 7.6 - 7.2 (m, 6H),, 2.21 (d, J = 1.3 Hz, 3H); GC-MS (t_R = 8.1 min; *m/z* 256 ([M^+])); HPLC (t_R = 15.8 min); LC-MS (t_R = 7.5 min; *m/z* 255 ([M-1]$^-$).

Synthetic Scheme for Compound 89 and Compound 90



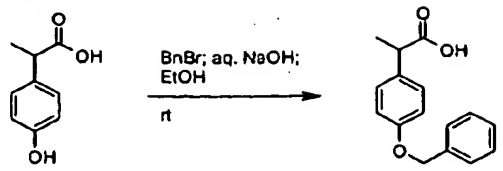
Experimental Section for Synthesis of Compound 89

2-(2-Phenoxy-phenyl)-propionic acid was synthesized in an analogous manner as for 2-biphenyl-4-yl-propionic acid (compound 55) from (2-phenoxy-phenyl)-acetic acid (327 mg; 1.43 mmol), LDA (2.0 M in heptane/THF/ethylbenzene; 1.50 mL; 3.0 mmol) and iodomethane (0.9 mL; 14.5 mmol) yielding 97 mg of pure product after purification by pRPLC (28%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 - 6.8 (m, 9H), 4.11 (q, J = 7.2 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H); HPLC (t_R = 12.2 min); LC-MS (t_R =5.7 min; *m/z* 241 ([M-1]$^-$).

Experimental Section for Synthesis of Compound 90

2-(4-Phenoxy-phenyl)-propionic acid was synthesized in an analogous manner as for 2-biphenyl-4-yl-propionic acid (compound 56) from (4-phenoxy-phenyl)-acetic acid (327 mg; 1.43 mmol), LDA (2.0 M in heptane/THF/ethylbenzene; 1.50 mL; 3.0 mmol) and iodomethane (0.9 mL; 14.5 mmol) yielding 19 mg of pure product after purification by pRPLC (5%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 - 6.9 (m, 9H), 3.73 (q, J = 7.2 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H); HPLC (t_R = 12.5 min); LC-MS (t_R = 5.8 min; *m/z* 241 ([M-1]$^-$).

Synthetic Scheme for Compound 91



Experimental Section for Synthesis of Compound 91

A soln of 2-(4-hydroxy-phenyl)-propionic acid (335 mg; 2.02 mmol), benzyl bromide (0.26 mL; 2.2 mmol), 1 M NaOH (6 mL; 6 mmol) and 95% ethanol (20 mL) was stirred at rt. After 20 h, the organic volatiles were removed on a rotary evaporator. The rxn was acidified with 1 M HCl (10 mL) then extracted with EtOAc (15 mL). The organic portion was washed with water (1 x 5 mL) and satd NaCl (2 x 5 mL), then dried over $MgSO_4$, filtered and concentrated to a white solid. The material was purified by flash chromatography (50 mL SiO_2/2:1 hexanes:EtOAc) yielding 308 mg (60%) of 2-(4-benzyloxy-phenyl)-propionic acid as a white solid. Rf 0.20 (2:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 - 7.2 (m, 7H), 6.94 (m, 2H), 5.05 (s, 2H), 3.70 (q, J = 7.2 Hz, 1H), 1.49 (d, J = 7.2 Hz, 3H); HPLC (t_R = 12.5 min); LC-MS (t_R = 5.6 min; *m/z* 255 ([M-1]$^-$; (ESI-)).

All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The mere mentioning of the publications and patent applications does not necessarily constitute an admission that they are prior art to the instant application.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious that

certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method of treating Alzheimer's disease comprising (1) identifying a patient having mild-to-moderate Alzheimer's disease and (2) administering to the patient a pharmaceutical composition comprising Alzheimer's disease treating effective amount of 2-(2-fluoro-biphenyl-4-yl)-2-methyl-propionic acid.

ABSTRACT

The invention provides novel compounds useful for the treatment of neurodegenerative disorders including Alzheimer's disease.

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Application Information

Title Line One::	Pharmaceutical Composition
Title Line Two::	And Method For Treating
Title Line Three::	Neurodegenerative Disorders
Application Type::	Provisional
Docket Number::	5062.00

Representative Information

Registration Number::	44,003
Registration Number::	49,022
Registration Number::	53,215
Registration Number::	52,943